Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Raener 2 mg/0.03 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: Ethinylestradiol, Dienogest

1 coated tablet contains:
Ethinylestradiol 0.03 mg
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 Raener 2 mg/0.03 mg Film-coated tablet should take into consideration the individual woman's current risk factors, particularly those for venous thromboembolism (VTE), and how the risk of VTE with Raener 2 mg/0.03 mg Film-coated tablet compares with other CHCs (see sections 4.3 and 4.4).

4.2 Posology and method of administration

Posology
With proper use of combined oral contraceptives, their failure is about 1% per year. If the tablet is missed or is taken incorrectly, the frequency of failure may increase.

How to take Raener 2mg/0.03 mg

Film-coated tablets are taken daily at the same time (if necessary with some fluid), according to the sequence printed on the blister pack. One film-coated tablet a day is taken for 21 consequent days. Each subsequent pack is started after 7 tablet-free days; usually a break-through bleeding occurs in this period. Typically, it starts 2-3 days after the last pill and may still be present when the first film-coated tablet from the next blister pack is taken.

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.

Long-term use is advisable, while respecting the principles applicable to the indication of contraception.

Method of administration

For oral use

How to start taking
• *No previous use of hormonal contraception in the last month:*
One film-coated tablet should be taken starting on the first day of the menstrual cycle (the first day of menstruation counting as Day 1). It can also be taken on the 2nd - 5th day of menstruation, but in this case additional barrier methods should be used during the first seven days of the first cycle.
• *Changing from a combined contraceptive (combined hormonal contraceptive, vaginal ring, transdermal patch)*
The woman should start with Raener 2mg/0.03 mg on the day following the usual tablet-free or placebo tablet interval of her previous COC or on the day after the last active tablet of her previous COC. In case a vaginal ring or transdermal patch has been used the woman should start using Raener 2mg/0.03 mg preferably on the day of removal, but at the latest when the next application would have been due.

• *Changing from a progestogen-only product (minipill, injection, implant) or from a progestogen-releasing intrauterine system (IUS)*

The woman may switch any day from the mini pill (from an implant or the IUS on the day of its removal, from an injectable when the next injection would be due), but should in all of these cases be advised to additionally use a barrier method for the first 7 days of tablet-taking.

• **After an abortion in the first trimester**

The woman may start immediately. When doing so, she does not need additional contraceptive measures.

• *After delivery or an abortion in the second trimester*

For breastfeeding women, see section 4.6 Fertility, pregnancy and lactation.
The woman should be advised to start at day 21 to 28 after delivery or an abortion in the second trimester. When starting later, the woman should be advised to additionally use a barrier method for the first 7 days. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of COC use or the woman has to wait for her first menstrual period.

Management of missed doses
The contraceptive effect of **Raener 2mg/0.03 mg** can be reduced if it is not taken regularly.
If the user is **less than 12 hours** late in taking any tablet, contraceptive protection is not reduced. The woman should take the tablet as soon as she remembers and should take further tablets at the usual time.
If the intake time is exceeded by **more than 12 hours**, contraceptive protection may be reduced. The management of missed tablets can be guided by the following two basic rules:

1. The intake of the tablets must never be discontinued for longer than 7 days;
2. 7 days of uninterrupted tablet-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian-axis.

Accordingly the following advice can be given for the everyday practice:

Week 1

The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. In addition, a barrier method such as a condom should be used for the

next 7 days. If intercourse took place in the preceding 7 days, the possibility of a pregnancy should be considered. The more tablets are missed and the closer they are to the regular tablet-free interval, the higher the risk of a pregnancy.

Week 2

The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. Provided that the woman has taken her tablets correctly in the 7 days preceding the first missed tablet, there is no need to use 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 tablet-free interval, the risk of reduced reliability of contraception is imminent. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. By adhering to either of the following two options, there is therefore no need to use additional contraceptive measures, provided that in the 7 days preceding the first missed tablet the woman has taken all tablets correctly. If this is not the case, she should follow the first of these two options and should use additional contraceptive measures for the next 7 days as well.
1. The user 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. 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 the woman missed tablets and subsequently has no withdrawal bleeding in the next tablet-free interval, the possibility of a pregnancy should be considered.

Management in case of vomiting or diarrhea
In case of severe gastrointestinal disturbances, absorption may not be complete and additional contraceptive measures should be taken.
If vomiting occurs within 3-4 hours after film-coated tablet intake, the advice concerning missed tablets as given in section Management of missed doses. is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra tablet(s) from another blister pack.

How to postpone a withdrawal bleed
To postpone the withdrawal bleed, the user should continue with another blister pack of Raener 2mg/0.03 mg without the usual tablet-free interval. The extension can be carried on for as long as wished until the end of the second pack. During the extension the woman may experience breakthrough bleeding or spotting. Regular intake of Raener 2mg/0.03 mg is then resumed after the usual 7-day tablet-free interval
To shift the withdrawal bleed to another day of the week than the woman is used to with her current scheme, she can be advised to shorten the tablet-free interval by as many days as she likes. 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
Raener 2mg/0.03 mg is only indicated after the menarche.

Elderly
Not applicable. Raener 2mg/0.03 mgis not indicated after the menopause.

Hepatic impairment

Raener 2mg/0.03 mg is contraindicated in women with severe liver disorders (see section 4.3 "Contraindications").

Renal impairment

Raener 2mg/0.03 mg 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
- Presence or history of hepatic disease, as long as liver function values have not returned to normal.
- Presence or history of liver tumors (benign or malignant)
- Known or suspected sex-steroid influenced malignancies (e.g. of genital organs or the breasts);
- Undiagnosed vaginal bleeding;
- Pregnancy or suspected pregnancy;
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1;

Raener 2mg/0.03 mg 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 Raener 2mg/0.03 mg 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 Raener 2mg/0.03 mg should be discontinued.

Circulatory Disorders

Risk of venous thromboembolism (VTE)

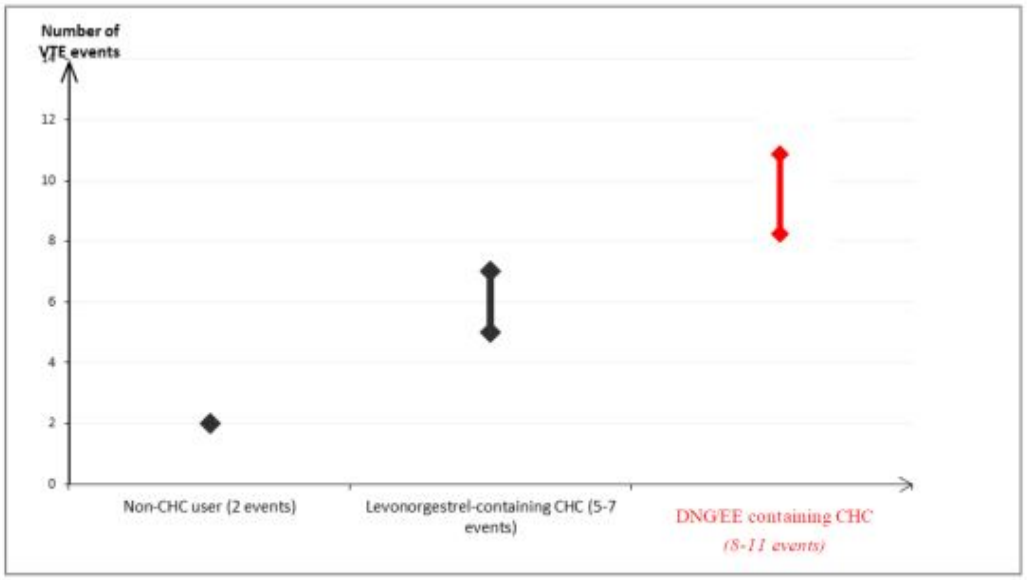
The use of any combined hormonal contraceptive (CHC) increases the risk of venous thromboembolism (VTE) compared with no use. **Products that contain levonorgestrel, norgestimate or norethisterone are associated with the lowest risk of VTE. Other products such as Raener 2mg/0.03 mgmay have up to 1.6 times this level of risk. The decision to use any product other than one known to have the lowest VTE risk should be taken only after a discussion with the woman to ensure she understands the risk of VTE with Raener 2mg/0.03 mg, 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 micrograms 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 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 women will develop a VTE in one year.
This 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.

[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 Raener 2mg/0.03 mg 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)

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).
Raener 2mg/0.03 mg 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	In these situations it is advisable to discontinue use of the pill (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilisation. Another method of

Note: temporary immobilisation including air travel >4 hours can also be a risk factor for VTE, particularly in women with other risk factors	contraception should be used to avoid unintentional pregnancy. Antithrombotic treatment should be considered if Raener 2mg/0.03 mg 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). Raener 2mg/0.03 mg 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 toseek 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

The most important risk factor for cervical cancer is a persistent HPV (human papilloma virus) infection. An increased risk of cervical cancer in long-term users of COCs has been reported in some studies, but there continues to be controversy about the extent to which this is attributable to the confounding effects of other factors identified such as cervical screening and sexual behaviour, including the use of barrier contraceptives.

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. 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.

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 tumor should be considered in the differential diagnosis when upper abdominal pain, enlarged liver or signs of intra-abdominal haemorrhage occur in women taking COCs.

Malignant tumours may be life-threatening or fatal.

Other conditions

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, it is preferable for the physician to discontinue the combined oral contraceptive and treat the hypertension as a precaution. Where considered appropriate, CHC use may be resumed if normotensive values can be achieved with antihypertensive therapy.

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, porphyria, systemic lupus erythematosus, haemolytic uraemic syndrome, Sydenham's chorea, gestational herpes, herpes gestationis, y 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 icterus 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.

Crohn's disease and ulcerative colitis may be associated with 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 this preparation.

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.

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

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 Raener 2mg/0.03 mg 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.
Significant improvement in acne symptoms usually occurs only after the 3rd cycle. Improvement of acne usually requires at least 3 months of treatment.

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).

Reduced cycle control

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 before COC use is continued.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take Raener 2mg/0.03 mg.

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.
Influence of other medicinal products on Raener 2mg/0.03 mg
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.
Enzyme induction can already be observed after a few days of treatment. Maximal enzyme induction is generally seen within a few weeks. After the cessation of drug therapy enzyme induction may be sustained for about 4 weeks.
Women on treatment with enzyme inducing drugs should temporarily use a barrier method or another method of contraception in addition to the COC. The barrier method must be used during the whole time of the concomitant drug therapy and for 28 days after its discontinuation.
If the drug therapy runs beyond the end of the active tablets in the COC pack, the placebo tablets must be discarded and the next COC pack should be started right away.

Substances increasing the clearance of COCs (diminished efficacy of COCs by enzyme-induction), e.g.:
Barbiturates, carbamazepine, phenytoin, primidone, rifampicin, and possibly also felbamate, griseofulvin, oxcarbazepine, topiramate and products containing the herbal remedy St. John's Wort (hypericum perforatum).
Raener 2mg/0.03 mg*Substances with variable effects on the clearance of COCs*
When co-administered with COCs, many combinations of HIV/ HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors, can increase or decrease plasma concentrations of estrogen or progestins. The net effect of these changes may be clinically relevant in some cases.
Raener 2mg/0.03 mgSubstances decreasing the clearance of COCs (enzyme inhibitors):
Dienogest is a substrate of cytochrome P450 (CYP) 3A4.

Potent and moderate CYP3A4 inhibitors such as azole antifungals (e.g. itraconazole, voriconazole, and fluconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice may increase the plasma concentrations of oestrogen or progestin or both hormones.
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 Raener 2mg/0.03 mg on other medicinal products
COCs may affect the metabolism of certain other active substances. Accordingly, plasma and tissue concentrations may either increase (e.g. cyclosporin) or decrease (e.g. lamotrigine).
However, based on in vitro data, an inhibition of CYP enzymes by dienogest is unlikely when used in therapeutic doses.

In vitro, ethinylestradiol is a reversible inhibitor of CYP2C19, CYP1A1 and CYP1A2 and a tightly bound inhibitor of CYP3A4/5, CYP2C8, and CYP2J2. In clinical trials, the administration of a hormonal contraceptive containing ethinylestradiol did not result in any or only modest increase in plasma concentrations of CYP3A4 substrates (e. g. midazolam), while plasma concentrations of CYP1A2 substrates may increase slightly (e. g. theophylline) or moderately (e. g. melatonin and tizanidine).

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, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs (see sections 4.3).

Therefore, Raener 2mg/0.03 mg-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. Raener 2mg/0.03 mg can be restarted 2 weeks following completion of treatment with these combination drug regimens.

Raener 2mg/0.03 mg*Other forms of interactions*
Laboratory tests

The use of steroids may influence the results of certain laboratory tests. Among these are: biochemical parameters of the liver, thyroid, adrenal and renal function, plasma levels of proteins (such as corticosteroid binding globulins) and lipid/lipoprotein fractions, carbohydrate metabolism, and parameters of coagulation and fibrinolysis. However, these changes remain within the normal range.

4.6 Fertility, pregnancy and lactation

Pregnancy
Raener 2mg/0.03 mg is not indicated during pregnancy.
If pregnancy occurs during intake of Raener 2mg/0.03 mg, 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.

The increased risk of VTE during the postpartum period should be considered when re-starting Raener 2mg/0.03 mg (see section 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. Therefore, the use of COCs should generally not be recommended until the breast-feeding mother has completely weaned her child. Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the milk.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The most commonly reported adverse reactions with taking Raener 2mg/0.03 mg in the indication of oral contraception or the treatment of moderate acne symptoms in women who also want contraception are abdominal pain and breast pain. They occur in ≥ 1% of users.
Severe adverse reactions are arterial and venous thromboembolism.

Adverse reactions in the indications of "oral contraception" and "treatment of mild to moderate acne manifestations in women who also want contraception".

The frequencies of adverse events with the use of Raener 2mg/0.03 mg for oral contraception and for the treatment of moderate acne in clinical trials (N = 4.942) are summarized in the following table. Within each group, adverse reactions are presented in order of decreasing seriousness.

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)
Very rare (<1/10,000)

Additional undesirable effects that only occurred during post-marketing studies and whose frequency cannot be estimated are listed under "not known".Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

See the table

System organ class (MedDRA v.12.0)	Common	Uncommon	Rare	Not Know
Infections and infestations		Vaginitis / vulvovaginitis, vaginal candidiasis or signals vulvo-vaginal yeast infections	Salpingo-oophoritis, urinary tract infections, cystitis, mastitis, cervicitis, fungal infections called candidiasis, labial herpes, influenza, bronchitis, sinusitis, upper respiratory infections,	

			viral infections	
Neoplasms, benign, malignant and unspecified (including cysts and polyps)			Uterine leiomyoma, breast lipoma	
Blood and lymphatic system disorders			Anemia	
Immune system disorders			Hypersensitivity	Exacerbation of symptomsof hereditary and acquired angioedema.
Endocrine disorders			Virilism	
Metabolism and nutrition disorders		Increased appetite	Anorexia	
Psychiatric disorders		Depressive mood	Depression, mental disorders, insomnia, sleep disturbances, aggressive reactions	Mood changes, reduced libido, increased libido
Nervous system disorders	Headaches	Migraines, dizziness	Ischemic stroke and cerebrovascular disorders, dystonia	
Eye disorders			Dry eye, eye irritation, oscillopsia, deterioration of vision	Contact lens intolerance
Ear and labyrinth disorders			sudden hearing loss, tinnitus, vertigo, hearing impairment	
Heart disorders			cardiovascular disorders, tachycardia [1]	
Vascular disorders		Hypotension, hypertension	Thrombophlebitis, VTE or ATE/pulmonary embolism, diastolic hypertension, orthostatic hypotension, flushing, varicose veins, venous disorders, veins pain	
Diseases of the respiratory tract, thoracic and mediastinal disorders			Asthma, hyperventilation	
Gastrointestinal disorders		Abdominal pain [2], nausea, vomiting, diarrhea	Gastritis, Enteritis, Dyspepsia	
Skin and subcutaneous tissue disorders		Acne, alopecia, rash[3], pruritus[4]	allergic dermatitis, atopic dermatitis / eczema, eczema, psoriasis, hyperhidrosis, chloasma, skin discoloration / hyperpigmentation, seborrhea, dandruff, hirsutism, skin lesions, skin reactions, orange peel, skin nevus	Urticaria, erythema nodosum, erythema multiforme
Musculoskeletal and connective tissue disorders			Back pain, musculoskeletal complaints, myalgia, pain in the extremities	
Reproductive system and breast disorders	Breast pain[5]	irregular	Cervical dysplasia, cysts	Breast gland

		menstrual bleeding[6], metrorrhagia[7], breast enlargement[8], breast edema, dysmenorrhea, vaginal discharge, ovarian cysts, pelvic pain	of the adnexa uteri pain of the adnexa uteri, breast cyst, fibrocystic breast disease, dyspareunia, galactorrhea, menstrual disorders	secretion
General disorders and complaints administration		Tiredness [9]	Chest pain, peripheric edema, influenz-like diseases, inflammation, pyrexia, irritability	Fluid retention
Investigations		Weight changes[10]	Increase in blood triglycerides, hypercholesterolemia	
Congenital, familial and genetic disorders			Manifestation of asymptomatic accessory breast	

[1] Including increased heart rate
2 Including the pain in the upper and lower abdomen, abdominal discomfort, bloating
[3] Includes rash maculares
[4] Including generalized pruritus
[5] Including breast symptoms and breast tenderness
[6] Including menorrhagia, hypomenorrhoe, oligomenorrhea and amenorrhea
[7] Consists of vaginal hemorrhage and metrorrhagia
[8] Including breast swelling / swelling
[9] Including asthenia and malaise
[10] Including weight gain, decrease and fluctuations
* Frequency estimated from epidemiological studies involving a group of combined contraceptives.
"Venous and arterial thromboembolic events" summarize the following medical units:
Peripheral deep venous occlusion, thrombosis and embolism/pulmonary vascular occlusion, thrombosis, embolism and heart attack/myocardial infarction/cerebral infarction and vascular event not specified as bleeding one

Description of selected adverse reactions

Adverse reactions with very low frequency or delayed onset of symptoms related to the group of combined oral contraceptives are listed below (see also "Contraindications" and "Special warnings and precautions for use").

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

Tumours
The frequency of diagnosis of breast cancer is very slightly increased among COC users. As breast cancer is rare in women under 40 years of age, the additional risk is small in relation to the overall risk of developing breast cancer. The causality with COC use is unknown..Liver tumors (benign and malignant)
Other *conditions*

Venous thromboembolic diseases
• Arterial thromboembolic diseases
• Cerebrovascular events
• Hypertension
• Hypertriglyceridemia
• Modification of the glucose tolerance or loading influencing the peripheral insulin resistance
• Liver tumors (benign and malignant)
• Hepatic dysfunction

• Chloasma

Occurrence or worsening of illnesses, not clarified their relationship with the use of COCs
is: jaundice and / or pruritus in connection with cholestasis; formation of gallstones; porphyria, systemic lupus erythematosus, haemolytic uraemic syndrome, Sydenham's chorea, herpes gestationis, otosclerosis related with hearing loss , Crohn's disease, ulcerative colitis, cervical cancer

The frequency of diagnosis of breast cancer is increased in users of oral contraceptives. Because breast cancer in women under 40 years rarely occurs, the number of additional diseases in comparison to the overall risk is small. A causal connection with the use of COCs is not known. For more information see section 4.3. and 4.4.

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

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

4.9 Overdose

There are no reports of serious harmful effects from overdose. The following symptoms may occur: nausea, vomiting and vaginal bleeding. Withdrawal bleeding may also occur in young girls who do not yet have menstruation and have accidentally taken this medicine. There are no antidotes and further treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens and estrogens, fixed combinations, dienogest and ethinylestradiol
ATC code: G03AA16

The contraceptive effective of Raener 2mg/0.03 mg is based on the combined interaction of different factors, where ovulation inhibition and changes in vaginal secretion are the most important.
In addition to protecting against pregnancy, COCs provide other benefits that, in addition to the negative properties (see Warnings and Precautions for Use, Adverse reactions) may be useful in deciding whether to choose this method of contraception. The cycle is more regular, menstruation is often less painful and bleeding is weaker. This may reduce the occurrence of iron deficiency.

The progestagenic component of Raener 2mg/0.03 mg, dienogest, is a potent progestagen and is considered to be the only nortestosterone derivative with antiandrogenic activity. Evidence of this antiandrogenic activity has been demonstrated in a clinical trial with patients suffering from inflammatory acne vulgaris.

Dienogest also shows a favourable lipid profile with an increase in the HDL component.

In addition, the risk reduction of endometrial and ovarian cancer has been proven. In addition, high-dose COCs (0.05 mg ethinylestradiol) reduce the incidence of ovarian cysts, pelvic inflammatory diseases, benign breast diseases and ectopic pregnancies. Whether this applies to low-dose COCs has not been confirmed yet.

5.2 Pharmacokinetic properties

Ethinylestradiol
Absorption
Ethinylestradiol is rapidly and fully absorbed following oral administration. Maximum serum concentrations of about 67 pg/ml, are reached approximately 1.5 to 4 hours after intake of a **Raener 2mg/0.03 mg** tablet.

During absorption and the first-pass metabolism in the liver, ethinylestradiol is extensively metabolized, resulting in a mean oral bioavailability of approximately 44%.

Distribution
Ethinylestradiol is pronounced (about 98 %) but is non-specifically bound to serum albumin and induces an increase in serum concentrations of sexual hormone binding globulin (SHBG). The absolute distribution of volume of ethinylestradiol is 2.8 to 8.6 l/kg.

Biotransformation
Ethinylestradiol is eliminated by presystemic conjugation in mucous membrane of the small intestine and the liver. Ethinylestradiol is primarily metabolized by aromatic hydroxylation; in that process different hydroxylated and methylated metabolites are formed, which are detectable as free metabolites or as a glucuronide sulphate conjugates in the serum. Ethinylestradiol is subjected to an enterohepatic circuit.

Elimination
The serum levels of ethinylestradiol decrease in two phases, characterized by half-life periods of about 1 hour and 10 – 20 hours.
Ethinylestradiol is not excreted in unchanged form. The metabolites are excreted in urine and the bile in a ratio of 4: 6.

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

Dienogest

Absorption
Orally administered dienogest is rapidly and almost completely absorbed. Maximum drug serum levels of . 51 ng/ml are reached at 2.5 hours of single intake of tablet. An absolute bioavailability of approximately 96% was detected in combination with ethinylestradiol..

Distribution
Dienogest binds to serum albumin, but it does not bind to SHBG or to corticosteroid-binding globulin (CBG). About 10% of the total serum drug concentration is present as free steroid,, e 90% is non-specifically bound to albumin. The ethinylestradiol-induced increase in SHBG does not influence the serum protein binding of dienogest.
Dienogest has an apparent volume of distribution of about 37-45 l.

Biotransformation
Dienogest is metabolized mainly through hydroxylation and conjugation with the formation of endocrinologically largely inactive metabolites These metabolites are quickly eliminated from plasma, so that, besides the unchanged dienogest in human plasma, no essential metabolite was found. The total clearance (Cl/F) after a single dose is 3.6 l/h.

Elimination
Dienogest has a half-life of 8.5-10.8 hours. Only negligible amounts of dienogest are excreted via the kidneys in unchanged form. Metabolites of dienogest are excreted in the urine and bile in a ratio of 3:1. Elimination half-life of metabolites is 14.4 hours.

Pharmacokinetic relationship

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

5.3 Preclinical safety data

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
Magnesium stearate
Maize starch
Povidone K-30

Film coating
Hypromellose 2910
Macrogol 400 (PEG)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30ºC.

Keep the blister in the outer carton in order to protect from the 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

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La Vallina s/n
Polígono Industrial Navatejera
Villaquilambre
Leon
24193
Spain

8 MARKETING AUTHORISATION NUMBER

PA1474/011/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10th August 2018
Date of last renewal: 19th December 2018

10 DATE OF REVISION OF THE TEXT

November 2024