SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Kelzyn 2mg/0,02 mg, tablet met verlengde afgifte

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

White prolonged-release tablets: Each tablet contains 2 mg of dienogest and 0.02 mg of ethinylestradiol.
Green placebo tablets: The tablet does not contain active substances.

Excipient(s) with known effect
Each prolonged-release white active tablet contains 19 mg lactose (as lactose monohydrate).
Each green placebo film-coated tablet contains 56 mg of lactose (as lactose monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablets.

The active tablet is a white, round tablet, of approximately 5 mm diameter.

The placebo tablet is a green, round tablet, of approximately 5 mm diameter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral hormonal contraception.

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

4.2 Posology and method of administration

Method of administration

Oral use.

Posology

The tablets must be taken every day at about the same time, if necessary with a little liquid, in the order shown on the blister pack. Tablet taking is continuous. One white tablet is to be taken daily for 24 consecutive days, followed by one green tablet for 4 days. Each subsequent pack is started the day after the last tablet of the previous pack. Withdrawal bleeding usually starts on day 2-3 after starting the green placebo tablets (last row) and may not have finished before the next pack is started.

How to start Kelzyn

- No preceding hormonal contraceptive use in the past month:

Tablet taking has to start on day one of the woman's natural cycle (i.e. the first day of her menstrual bleeding). 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.

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

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

- Switching from a progestogen-only method (progestin-only pill, implants, injectable forms) or from a progestogen-releasing intrauterine system (IUS):

The woman may switch any day from the progestogen-only 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.

- Following first-trimester abortion:

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

- After delivery or second-trimester abortion:

Women should be advised to start at day 21 to 28 after delivery or second-trimester abortion. 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.

For breastfeeding women, see section 4.6.

Management of missed tablets

Contraceptive reliability may be reduced if white tablets are missed, and particularly if tablets are missed during the first days of the pack.

If the woman is **less than 24 hour** late in taking the white active tablet, pregnancy 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 woman is more **than 24 hours late** in taking any white active tablet, pregnancy protection may be reduced. Missed tablet may then be managed according to the following two basic rules:

1. The recommended interval with hormone-free tablets is 4 days, intake of active tablets should never be interrupted for more than 4 days.
2. Seven days of uninterrupted intake of active tablets is required to adequately inhibit the hypothalamic-pituitary-ovarian axis to obtain ovulation inhibition.

Therefore, the following instructions can be given in clinical practice:

- Day 1-7

The user should take the last missed tablet as soon as possible, 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 until she has completed 7 days of uninterrupted white active tablet-taking. If intercourse took place in the preceding 7 days, the possibility of a pregnancy should be considered. The more tablets are missed and the closer they are to the placebo tablet phase, the higher the risk of a pregnancy.

- Day 8-14

The user should take the last missed tablet as soon as possible, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. Provided that the woman has taken her tablets correctly in the 7 days preceding the first missed tablet, there is no need to use extra

contraceptive precautions. However, if she has missed more than 1 tablet, the woman should be advised to use extra precautions until she has completed 7 days of uninterrupted white active tablet-taking.

- Day 15-24

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

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

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

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

Errors in taking one or more green tablets have no consequence, provided the interval between the last white tablet of the current pack and the first white tablet of the following pack does not exceed four days. Missed placebo tablets should be discarded, to avoid a longer hormone-free interval than 4 days.

Advice in case of gastrointestinal disorders

In case of severe gastro-intestinal disturbances (e.g., vomiting or diarrhoea), absorption may not be complete and additional contraceptive measures should be taken. If vomiting occurs within 3-4 hours after white active tablet-taking, a new (replacement) tablet should be taken as soon as possible. The new white active tablet should be taken within 24 hours of the usual time of tablet-taking if possible. If more than 24 hours elapse, the advice concerning missed tablets, as given in section 4.2 "*Management of missed tablets*", is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra white active tablet(s) from another blister pack.

Postponing a scheduled bleed

To delay a period the woman should continue with the next blister pack of Kelzyn without taking the green placebo tablets from her current pack. The intake can be carried on for as long as wished, at most until the end of the second pack. During intake of the second pack the woman may experience unscheduled bleeding or spotting. Regular intake of Kelzyn is then resumed after the usual 4 days placebo intake interval.

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

Additional information for special patient groups

Paediatric population
Kelzyn is only indicated after menarche (see section 5.1).

Elderly patients
Not applicable. Kelzyn is not indicated after menopause.

Patients with hepatic impairment
Kelzyn is contraindicated in women with severe hepatic diseases (see section 4.3).

Patients with renal impairment
Kelzyn has not been specifically studied in patients with impaired renal function. Available data do not suggest a change in treatment in this patient population.

4.3 Contraindications

Combined hormonal contraceptives (CHCs) should not be used in the following conditions. Should any of the listed conditions appear for the first time during CHC use, the product must be stopped immediately.

- hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- presence or risk of venous thromboembolism (VTE)
    - venous thromboembolism – current VTE (on anticoagulants) or history of (e.g. deep venous thrombosis [DVT] or pulmonary embolism [PE])
    - known hereditary or acquired predisposition for venous thromboembolism, such as APC-resistance, (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency
    - major surgery with prolonged immobilisation (see section 4.4)
    - a high risk of venous thromboembolism due to the presence of multiple risk factors (see section 4.4)
- presence or risk of arterial thromboembolism (ATE)
    - arterial thromboembolism – current ATE, history of ATE (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 severe hepatic disease as long as liver function values have not returned to normal
- presence or history of liver tumours (benign or malignant)
- known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts)
- undiagnosed vaginal bleeding

Kelzyn is contraindicated for concomitant use with the medicinal products containing ombitasvir/paritaprevir/ritonavir, dasabuvir, glecaprevir/pibrentasvir and 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 Kelzyn 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 Kelzyn should be discontinued.

In case of suspected or confirmed thrombosis the CHC must be discontinued. In case anticoagulant 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 CHC products, including Kelzyn, may have a slightly higher 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 Kelzyn, 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 hormonal 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 low dose CHC that contains levonorgestrel about 6[1] will develop a VTE in one year.

Data from studies of women using CHC containing dienogest and ethinylestradiol 2 mg/0.03 mg, estimated[2] that out of 10,000 women between 8 and 11 women will develop a VTE in one year.

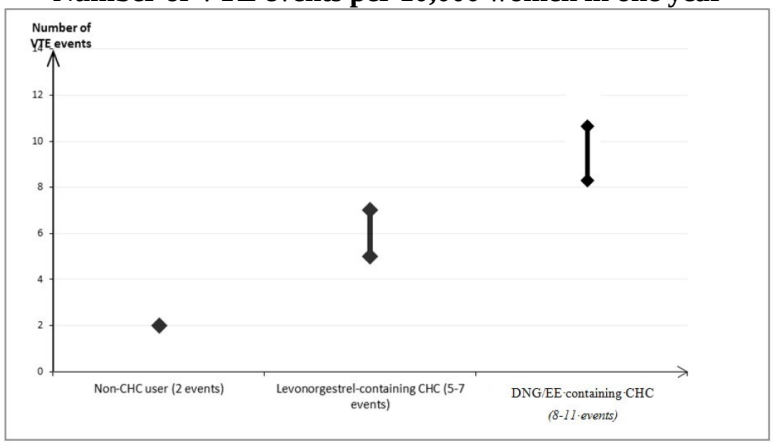
This number of VTEs per year is fewer than the number expected during pregnancy or in the postpartum period.

VTE may be fatal in 1-2% of the 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 for dienogest/ethinylestradiol 2 mg/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 1).

Kelzyn 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 1: Risk factors for VTE

Risk factor	**Comment**
Obesity (body mass index over 30 kg/m²)	Risk increases substantially as BMI rises. Particularly important to consider if other risk factors also present.
Prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma Note: temporary immobilisation including air travel >4 hours can also be a risk factor for VTE, particularly in women with other risk factors	In these situations it is advisable to discontinue use of the tablet (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilisation. Another method of contraception should be used to avoid unintentional pregnancy. Antithrombotic treatment should be considered if Kelzyn 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 2). Kelzyn 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 2: 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

Tumours

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

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using COCs. During the course of 10 years after cessation of COC use this increased risk gradually returns to the age-related background risk. 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 intraabdominal haemorrhages. A hepatic tumour 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, COC 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, otosclerosis-related hearing loss.

Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.

Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal. Recurrence of cholestatic icterus 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 medicinal product.

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.

Medical examinations / consultation
Prior to the initiation or reinstitution of Kelzyn a complete medical history (including family history) should be taken and pregnancy must be ruled out. Blood pressure should be measured and a physical examination should be performed, guided by the contra-indications (see section 4.3) and warnings (see section 4.4). It is important to draw a woman's attention to the information on venous and arterial thrombosis, including the risk of Kelzyn 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.

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).

Cycle control
With all COCs, irregular bleeding (spotting or unscheduled 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, scheduled bleeding may not occur during the placebo tablet phase. 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.

Based on women's diaries from clinical trials, the percentage of women per cycle experiencing unscheduled bleeding during cycles 2-6 was 50.5%. The percentage of women per cycle experiencing unscheduled bleeding during cycles 2-9 was 41.7%.

The percentage of women who discontinued the phase III studies LPRI424-301 and 302 in EU due to an AE related to bleeding was 1.7%.

The proportion of subjects with prolonged bleeding (>10 consecutive days) for Kelzyn was 5.6 % during cycles 2-9.

Users of Kelzyn may experience no bleeding although not being pregnant. Based on patient diaries from a comparative clinical trial, no bleeding occurs in approximately 10.5% of subjects during cycles 2-9.

Kelzyn contains lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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

Effects of other medicinal products on Kelzyn
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 hepatic 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 concomitant drug administration and for 28 days after its discontinuation. If the drug therapy runs beyond the end of the tablets in the COC pack, the placebo tablets must be discarded and the next COC pack should be started right away.

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

Substances increasing the clearance of COCs (diminished efficacy of COCs by enzyme-induction), e.g.:
Barbiturates, carbamazepine, phenytoin, primidone, rifampicin and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin 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 of HIV/HCV protease inhibitors and nonnucleoside reverse transcriptase inhibitors as well as combinations of both can increase or decrease plasma concentrations of estrogen or progestin. 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 nonnucleoside reverse transcriptase inhibitor therapy.

Substances decreasing the clearance of COC (enzyme inhibitors)
Dienogest is a substrate of cytochrome P450 (CYP) 3A4. 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 COC containing 0.035 mg ethinylestradiol.

Effects of Kelzyn 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).

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 medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequently in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs). Additionally, also in patients treated with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs (see section 4.3).

Therefore, Kelzyn 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. Kelzyn 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

Kelzyn is not indicated during pregnancy.

If pregnancy occurs during use of Kelzyn, the treatment should be withdrawn 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 COCs were taken inadvertently during pregnancy.

Animal studies have shown adverse effects during pregnancy and lactation (see section 5.3). Based on these animal data, an adverse effect due to hormonal action of the active compounds cannot be excluded. However, general experience with COCs during pregnancy did not provide evidence for an actual adverse effect in humans.

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

Breastfeeding

Lactation may be influenced by COCs as they may reduce the quantity and change the composition of breast milk. Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the milk during COC use. These amounts may affect the child. Therefore, Kelzyn should not be used until the nursing mother has completely weaned her child.

Fertility

Kelzyn is indicated for oral contraception. For information on return to fertility, see section 5.1.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. No effects on ability to drive and use machines have been observed in users of COCs.

4.8 Undesirable effects

The most commonly reported adverse reactions with <dienogest/ ethinylestradiol 2/ 0.02 mg> during the clinical trials (1719 women) were metrorrhagia (8.4%), headache (3.7%) and breast pain (3.5%).

Changes in the bleeding pattern was an adverse reaction frequently reported in the clinical trials (see section 5.1).

Tabulated list of adverse reactions

The table below reports adverse reactions (ADRs) by MedDRA system organ classes (MedDRA SOCs). The frequencies are based on clinical trial data. All adverse reactions that have been reported in clinical trials with dienogest/ ethinylestradiol 2/ 0.02 mg are listed. All ADRs listed in the category 'rare' occurred only once (in 1 volunteer) resulting in < 0.1%.

The frequencies of adverse reactions are based on the following categories: Very common (≥ 1/10)

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), Not known (cannot be estimated from the available data).

System Organ Class (MedDRA)	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1,000 to < 1/100)**	**Rare (≥ 1/10,000 to < 1/1,000)**	**Not known**
Infections and infestations	Vaginal infection [1]	Urinary tract infection[2]	Genital herpes Myringitis	
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Fibroadenoma of breast	
Blood and lymphatic system disorders			Leukopenia	
Immune system disorders				Exacerbation of symptoms of hereditary and acquired angioedema
Endocrine disorders		Hypothyroidism	Hyperthyroidism	
Metabolism and nutrition disorders		Appetite disorder [3] Hyperglycaemia	Dyslipidaemia Fluid retention	
Psychiatric disorders	Libido disorder [4] Mood disturbances [5]	Anxiety [6] Depressed mood Depression Mental disorder [7] Sleep disorder [8]		
Nervous system disorders	Headache [9]	Migraine [10] Dizziness	Dysgeusia Hypoaesthesia Paraesthesia	
Eye disorders			Eye pruritus Visual impairment	
Ear and labyrinth disorders			Vertigo	
Cardiac disorders			Palpitations	
Vascular disorders		Hypertension [11]Thrombotic events[12]	Blood pressure fluctuation Haematoma Hot flush Spider vein Varicose vein	
Respiratory, thoracic and mediastinal disorders			Epistaxis	
Gastrointestinal disorders	Nausea Abdominal pain [13]	Vomiting Diarrhoea Flatulence Abdominal distension	Constipation Dyspepsia Gastrooesophageal reflux disease Hyperaesthesia teeth	
Skin and subcutaneous tissue disorders	Acne	Alopecia Pruritus Dermatitis [14] Hyperhidrosis [15] Rash [16]	Chloasma Dry skin Skin disorder Urticaria	

Musculoskeletal and connective tissue disorders		Pain in extremity	Arthralgia	
Renal and urinary disorders			Haematuria, Leukocyturia	
Reproductive system and breast disorders	Metrorrhagia [17] Breast discomfort [18] Dysmenorrhoea [19]	Amenorrhoea Vaginal haemorrhage Ovarian cyst Vulvovaginal dryness Pelvic pain, Vulvovaginal pruritus Cervical dysplasia Dyspareunia Menstrual disorder[20] Vaginal discharge Vulvovaginal inflammation	Endometrial hyperplasia Genital discomfort	
General disorders and administration site conditions		Fatigue Oedema peripheral Swelling [21]	Discomfort Sluggishness General physical health deterioration	
Investigations	Weight increased [22] Blood thyroid stimulating hormone increased Blood triglycerides increased [23]	Blood creatine phosphokinase increased Blood cholesterol increased[24] Hepatic enzyme increased [25] Weight decreased	Blood lactate dehydrogenase increased Blood potassium increased Blood pressure abnormal Blood prolactin increased Fibrin D dimer increased Insulin resistance test	

1. Including vulvovaginal mycotic infection, vulvovaginal candidiasis and bacterial vaginosis
2. Including bacteriuria
3. Including decreased appetite and increased appetite
4. Including loss of libido and sexual aversion disorder
5. Including mood swings, mood altered, Irritability, Affect lability, affective disorder, listless and apathy.
6. Including anxiety disorder, Nervousness, Restlessness, Dysphoria, and tension
7. Including mental impairment, borderline personality disorder, and panic attack
8. Including insomnia and somnolence
9. Including tension headache
10. Including migraine with aura
11. Including blood pressure increased
12. Including deep vein thrombosis, venous thrombosis and pulmonary embolism
13. Including abdominal pain lower and abdominal pain upper
14. Including dermatitis atopic, dermatitis allergic, perioral dermatitis
15. Including night sweats
16. Including rash macular
17. Including uterine hemorrhage
18. Including breast pain, Breast engorgement, breast enlargement and breast tenderness
19. Including premenstrual pain
20. Including oligomenorrhea, menstruation irregular, menorrhagia, polymenorrhoea
21. Including peripheral swelling, generalised oedema and swelling
22. Including obesity
23. Including hypertriglyceridemia
24. Including Hypercholesterolemia
24. Including ALT increased, AST increased, GGT increased

Description of selected adverse reactions

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

The following serious adverse events have been reported in women using COCs, which are discussed in section 4.4.

Tumours

- The frequency of diagnosis of breast cancer is slightly increased among COC users. As breast cancer is rare in women under 40 years of age, the additional risk is small in relation to the overall risk of developing breast cancer. Causation with COC use is unknown.
- Liver tumours
- 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: cholestatic icterus, gallstone formation, porphyria, systemic lupus erythematosus, haemolytic 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
Unscheduled bleeding and/or contraceptive failure may result from interactions of other drugs (enzyme inducers) with oral contraceptives (see section 4.5).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

The acute oral toxicity of ethinylestradiol and dienogest is very low. If, for example, a child takes several Kelzyn 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 unexpected 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: Sex hormones and modulators of the genital system, hormonal contraceptives for systemic use, progestogens and estrogens, fixed combinations
ATC Code: G03AA16

Mechanism of action

The contraceptive effect of Kelzyn is based on the interaction of various factors, the most important of which are seen as the inhibition of ovulation.

Kelzyn contains dienogest and ethinylestradiol. Dienogest is a nortestosterone derivative with no androgenic but rather an antiandrogenic activity of approximately one third of that of cyproterone acetate. Dienogest binds to the progesterone receptor of the human uterus with only 10% of the

relative affinity of progesterone. Despite its low affinity to the progesterone receptor, dienogest has a strong progestogenic effect in vivo. Dienogest has no significant androgenic, mineralocorticoid or glucocorticoid activity in vivo.

Ethinylestradiol is a potent orally active synthetic estrogen widely used in contraceptive products.

Clinical efficacy and safety

Two multicenter Phase III European clinical trials were performed with Kelzyn. In the pooled analysis of these two studies the following Pearl Index values (upper limit 95% confidence interval (CI)) were calculated:

Pearl Index (18-35 years of age), user + method failure: 0.2 (upper limit 95% CI 0.77).

Pearl Index (18-45 years of age), user + method failure: 0.2 (upper limit 95% CI 0.64).
The Pearl Index was calculated based on the number of exposure cycles generated in the European Phase III clinical trials. The exposure cycle was defined as a 28-day cycle, where at least one treatment diary entry of Kelzyn intake is available. In addition, a cycle is an exposure cycle if the subject becomes pregnant during this cycle regardless of whether this cycle is a 28-day cycle or not.

Pearl Indices for Kelzyn users in pooled LPRI-424/301 and LPRI-424/302 trials

A total of 2 confirmed on-drug pregnancies including one method failure pregnancy and one user failure pregnancy, were observed in women who used Kelzyn up to 13x28-day cycles in LPRI-424/301 and LPRI-424/302 trials. Both pregnancies were reported for subjects ≤ 35 years. In the following table an overview of number of cycles and overall PIs, PIs based on evaluable cycles and method failure PIs (confirmed pregnancies) is presented for all women and for women aged ≤ 35 years.

	Kelzyn	
	Women Aged ≤ 35 Years	**All Women**
	N = 1309	**N = 1576**
Overall Pearl Index		
Total number of exposure cycles	12126	14597
Confirmed on-drug pregnancy (n [%])	2 (0.2)	2 (0.1)
Pearl Index (95% CI)	0.2 (0.03, 0.77)	0.2 (0.02, 0.64)
Pearl Index for evaluable cycles		
Total number of evaluable cycles	9624	11808
Confirmed on-drug pregnancy (n [%])	2 (0.2)	2 (0.1)
Pearl Index (95% CI)	0.3 (0.03, 0.98)	0.2 (0.03, 0.8)
Pearl Index for method failures		
Total number of perfect cycles	6415	8006
Confirmed on-drug pregnancy (n [%])	2 (0.2)	2 (0.1)
Pearl Index (95% CI)	0.4 (0.05, 1.46)	0.3 (0.04, 1.17)

The cumulative 13-cycle pregnancy ratio (95% CI) of all Kelzyn users (FAS) in both trials was 0.15 (0.00, 0.36), and that of the age subgroup ≤ 35 years was 0.18 (0.00, 0.43).

Paediatric population
There are limited clinical data on efficacy and safety for the use of COCs in adolescents under 18 years of age.

The European Medicines Agency has deferred the obligation to submit the results of studies with Kelzyn in one or more subsets of the paediatric population in condition, as per paediatric investigation plan (PIP) decision, for the granted indication (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Ethinylestradiol
Absorption
The mean oral bioavailability of ethinylestradiol is about 45%, with a large interindividual variation of about 20-65%. The plasma profiles following repeated daily doses of prolonged release formulation (2mg dienogest and 20µg ethinylestradiol) were characterised by a mean Cmax of 64 pg/mL ethinylestradiol observed at a t_{max} of 3.8 hours. The observed AUC0-24h was 706 pg×h/mL ethinylestradiol. In comparison to the immediate release formulation, t_{max} was observed later, 3.8 hours (PR) compared to 1.3 hours (IR). Food has no effect on the PK profile of Kelzyn.

Distribution
Ethinylestradiol is highly but non-specifically bound to serum albumin (approximately 98%) and induces an increase in the serum concentrations of SHBG (sex hormone-binding globulin). The apparent volume of distribution for an oral dose of 0.03 mg after a single administration is between 576-625 L.

Biotransformation
Ethinylestradiol is subject to presystemic conjugation in both small bowel mucosa and the liver. Ethinylestradiol is primarily metabolized by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed. These are present as free metabolites and as conjugates with glucuronides and sulfate.

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

Dienogest
Absorption
Dienogest has a high oral bioavailability of over 90%. The plasma profiles following repeated daily doses of prolonged release formulation (2mg dienogest and 20µg ethinylestradiol) were characterised by a mean C_{max} of 59 ng/mL dienogest observed at a t_{max} of 3.8 hours. The observed AUC_{0-24h} was 732 ng×h/mL dienogest. In comparison to the immediate release formulation, the AUC_{0-24h} was similar but the Cmax was lower and observed later following repeated administration of prolonged release formulation.
Food has no effect on the PK profile of Kelzyn.

Distribution
Dienogest is bound to serum albumin and does not bind to SHBG or corticoid binding globulin (CBG). About 10% of the total serum drug concentrations are present as free steroid. 90% are nonspecifically 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 about 40 l after a single oral dose of 1 mg.

Biotransformation

Dienogest is metabolized predominantly through hydroxylation and conjugation, with the formation of endocrinologically largely inactive metabolites. These metabolites are very quickly cleared from plasma so that in human plasma no important metabolite is observed besides unchanged dienogest.

Elimination
Dienogest is excreted at a urinary to faecal ratio of about 3:1 after oral administration of 0.1 mg/kg, The serum clearance of dienogest is ~ 64 ml/min, and the $t_{1/2}$ for excretion of urinary metabolites is ~14 h. Most of the metabolites are eliminated in the first 24 h, and approximately 86% of the administered dose is eliminated within 6 days.

5.3 Preclinical safety data

Preclinical studies with ethinylestradiol and dienogest revealed the expected estrogenic and progestagenic effects.

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

Environmental risk assessment studies have shown that dienogest and ethinylestradiol may pose a risk to the aquatic environment (see section 6.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

White tablet (active):
Lactose monohydrate
Hypromellose (E 464)
Povidone
Magnesium stearate (E 470b)
Silica colloidal anhydrous

Coating
Polyvinyl alcohol-partially hydrolyzed
Titanium dioxide (E 171)
Macrogol (E 1521)
Talc (E 553b)

Green tablet (placebo):
Lactose monohydrate
Maize starch
Povidone
Silica, colloidal
Magnesium stearate (E 470b)

Coating
Hypromellose (E 464)
Triacetin (E 1518)
Polysorbate 80
Titanium dioxide (E 171)
Indigo carmine aluminium lake
Iron oxide yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Keep the blister in the outer carton, in order to protect from light.

6.5 Nature and contents of container

Blister pack (PVC-PE-PVDC /Aluminium) containing 24 white tablets and 4 green tablets.

The pack sizes are 1 x 28, 3 x 28, 6 x 28 and 13 x 28.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. This medicinal product may pose a risk to the environment (see section 5.3).

7. MARKETING AUTHORISATION HOLDER

Exeltis Healthcare S.L.
Avda. de Miralcampo 7,
Pol. Ind. Miralcampo, 19200
Azuqueca de Henares (Guadalajara)
Spain

8. MARKETING AUTHORISATION NUMBER(S)

RVG 131206

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van der vergunning: 20 maart 2024

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft rubriek 6.1: 12 september 2025

<Detailed information on this medicinal product is available on the website of {name of Member State Agency (link)}>