SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Qlaira film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each wallet (28 film-coated tablets) contains in the following order:
2 dark yellow tablets each containing 3 mg estradiol valerate
5 medium red tablets each containing 2 mg estradiol valerate and 2 mg dienogest
17 light yellow tablets each containing 2 mg estradiol valerate and 3 mg dienogest
2 dark red tablets each containing 1 mg estradiol valerate

2 white tablets do not contain active substances

Excipient with known effect:

Each dark yellow film-coated tablet contains 45.942 mg lactose (as monohydrate)
Each medium red tablet contains 44.992 mg lactose (as monohydrate)
Each light yellow tablet contains 44.042 mg lactose (as monohydrate)
Each dark red tablet contains 47.842 mg lactose (as monohydrate)
Each white tablet contains 49.538 mg lactose (as monohydrate)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Dark yellow film-coated tablet, round with biconvex faces, one side is marked with the letters “DD” in a regular hexagon

Medium red film-coated tablet, round with biconvex faces, one side is marked with the letters “DJ” in a regular hexagon

Light yellow film-coated tablet, round with biconvex faces, one side is marked with the letters “DH” in a regular hexagon

Dark red film-coated tablet, round with biconvex faces, one side is marked with the letters “DN” in a regular hexagon

White film-coated tablet, round with biconvex faces, one side is marked with the letters “DT” in a regular hexagon

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral contraception.

Treatment of heavy menstrual bleeding in women without organic pathology who desire oral contraception.

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

4.2 Posology and method of administration

Method of administration

Oral use

Posology

How to take Qlaira

Tablets must be taken in the order directed on the package every day at about the same time with some liquid as needed. Tablet taking is continuous. One tablet is to be taken daily for 28 consecutive days. Each subsequent pack is started the day after the last tablet of the previous wallet. Withdrawal bleeding usually starts during the intake of the last tablets of a wallet and may not have finished before the next wallet is started. In some women, the bleeding starts after the first tablets of the new wallet are taken.

How to start Qlaira

- No preceding hormonal contraceptive use (in the past month)

Tablet-taking has to start on day 1 of the woman's natural cycle (i.e. the first day of her menstrual bleeding).

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

The woman should start with Qlaira on the day after the last active tablet (the last tablet containing the active substances) of her previous COC. In case a vaginal ring or transdermal patch has been used, the woman should start using Qlaira on the day of removal.

- Changing from a progestogen-only method (progestogen-only pill, injection, implant) 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 **9 days** of tablet-taking.

- Following first-trimester abortion

The woman may start immediately. When doing so, she needs not take additional contraceptive measures.

- Following delivery or second-trimester abortion

For breastfeeding women see section 4.6.

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 **9 days** of tablet-taking. 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 tablets

Missed (white) placebo tablets can be disregarded. However, they should be discarded to avoid unintentionally prolonging the interval between active tablet-taking.

The following advice only refers to missed active tablets:

If the woman 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 she is **more than 12 hours** late in taking any tablet, contraceptive protection may be reduced.

Depending on the day of the cycle as indicated in the current wallet on which the tablet has been missed (see table below for details), the following principles on tablet intake and **back-up contraceptive measures** (e.g. a barrier method such as a condom) apply:

DAY	**Color** Content of estradiol valerate (EV)/dienogest (DNG)	**Principles to follow if missing *<u>one</u>* tablet for more than 12 hours:**
1-2	**Dark yellow tablets** (3.0 mg EV)	- Take the missed tablet immediately - Take the next tablet at the same time as usual (even if this means taking two tablets at the same day) - Continue taking one tablet each day at the same time as usual - Use back-up contraception **for the next 9 days**
3-7	**Medium red tablets** (2.0 mg EV + 2.0 mg DNG)	
8-17	**Light yellow tablets** (2.0 mg EV + 3.0 mg DNG)	
18-24	**Light yellow tablets** (2.0 mg EV + 3.0 mg DNG)	- Do not take the missed tablet and discard the current wallet - Take the first tablet of a new wallet - Continue taking one tablet each day from the new wallet at the same time as usual - Use back-up contraception **for the next 9 days**
25-26	**Dark red tablets** (1.0 mg EV)	- Take the missed tablet immediately - Take the next tablet at the same time as usual (even if this means taking two tablets at the same day) - Continue taking one tablet each day at the same time as usual - No back-up contraception necessary
27-28	**White tablets** (Placebos)	- Discard the missed tablet - Take the next tablet at the same time as usual - When the last tablet is missed in the current wallet, continue

		taking the first tablet from the new wallet at the same time as usual - No back-up contraception necessary

Not more than two tablets are to be taken on a given day.

If a woman has forgotten to start a new wallet, or if she has missed one or more tablets during days 3 -9 of the wallet, she may already be pregnant (provided she has had intercourse in the 7 days before the oversight). The more tablets (of those with the two combined active ingredients on days 3-24) that are missed and the closer they are to the placebo tablet phase, the higher the risk of a pregnancy.

If the woman missed tablets and subsequently has no withdrawal bleed at the end of the wallet /beginning of new wallet, the possibility of a pregnancy should be considered.

Advice in case of gastro-intestinal disturbances

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 active tablet-taking, the next tablet should be taken as soon as possible. This tablet should be taken within 12 hours of the usual time of tablet-taking, if possible. If more than 12 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 corresponding tablet(s) needed from another pack.

Additional information on special populations

Children and adolescents

No data available for use in adolescents below 18 years.

Geriatric patients

Qlaira is not indicated after menopause.

Patients with hepatic impairment

Qlaira is contraindicated in women with severe hepatic diseases. See also section 4.3.

Patients with renal impairment

Qlaira has not been specifically studied in renally impaired patients.

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 use, the product should be stopped immediately.

- Presence or risk of venous thromboembolism (VTE)
  - Venous thromboembolism – current VTE (on anticoagulants) or history of (e.g. deep venous thrombosis [DVT] or pulmonary embolism [PE])

- Known hereditary or acquired predisposition for venous thromboembolism, such as APC-resistance, (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency
- Major surgery with prolonged immobilisation (see section 4.4)
- A high risk of venous thromboembolism due to the presence of multiple risk factors (see section 4.4)

- Presence or risk of arterial thromboembolism (ATE)
  - Arterial thromboembolism – current arterial thromboembolism, history of arterial thromboembolism (e.g. myocardial infarction) or prodromal condition (e.g. angina pectoris)
  - Cerebrovascular disease – current stroke, history of stroke or prodromal condition (e.g. transient ischaemic attack, TIA)
  - Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant).
  - History of migraine with focal neurological symptoms.
  - A high risk of arterial thromboembolism due to multiple risk factors (see section 4.4) or to the presence of one serious risk factor such as:
    - diabetes mellitus with vascular symptoms
    - severe hypertension
    - severe dyslipoproteinaemia
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
- Presence or history of liver tumours (benign or malignant).
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts).
- Undiagnosed vaginal bleeding.
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Warnings

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

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

The following warnings and precautions are mainly derived from clinical and epidemiological data of *ethinyl estradiol* containing COCs.

- 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. Limited data suggests that Qlaira may have a risk of VTE in the same range. The decision to use any other product (such as Qlaira) 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 CHCs, 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 (<50 µg ethinylestradiol) combined hormonal contraceptives have found that out of 10,000 women between about 6 and 12 will develop a VTE in one year

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

Limited epidemiological evidence suggests that the risk of VTE with the use of Qlaira may be in the same range as the risk with other CHCs, including CHCs containing levonorgestrel.

The number of VTEs per year with low dose CHCs is fewer than the number expected in women during pregnancy or in the postpartum period.

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

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).

Qlaira is contraindicated if a woman has multiple risk factors that put her at high risk of venous thrombosis (see section 4.3). If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors – in this case her total risk of VTE should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed (see section 4.3).

Table: Risk factors for VTE

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

[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

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). Qlaira is contraindicated if a woman has one serious or multiple risk factors for ATE that puts her at high risk

of arterial thrombosis (see section 4.3). If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors - in this case her total risk should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed (see section 4.3).

Table: Risk factors for ATE

Risk factor	**Comment**
Increasing age	Particularly above 35 years
Smoking	Women should be advised not to smoke if they wish to use a CHC. Women over 35 who continue to smoke should be strongly advised to use a different method of contraception.
Hypertension	
Obesity (body mass index over 30 kg/m^2)	Risk increases substantially as BMI increases. Particularly important in women with additional risk factors
Positive family history (arterial thromboembolism ever in a sibling or parent especially at relatively early age e.g. below 50).	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use
Migraine	An increase in frequency or severity of migraine during CHC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation
Other medical conditions associated with adverse vascular events	Diabetes mellitus, hyperhomocysteinaemia, valvular heart disease and atrial fibrillation, dyslipoproteinaemia and systemic lupus erythematosus.

Symptoms of ATE

In the event of symptoms women should be advised to seek urgent medical attention and to inform the healthcare professional that she is taking a CHC.

Symptoms of a cerebrovascular accident can include:

- sudden numbness or weakness of the face, arm or leg, especially on one side of the body
- sudden trouble walking, dizziness, loss of balance or coordination
- sudden confusion, trouble speaking or understanding
- sudden trouble seeing in one or both eyes
- sudden, severe or prolonged headache with no known cause
- loss of consciousness or fainting with or without seizure.

Temporary symptoms suggest the event is a transient ischaemic attack (TIA).

Symptoms of myocardial infarction (MI) can include:
- pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm, or below the breastbone
- discomfort radiating to the back, jaw, throat, arm, stomach
- feeling of being full, having indigestion or choking
- sweating, nausea, vomiting or dizziness
- extreme weakness, anxiety, or shortness of breath
- rapid or irregular heartbeats.

Tumours

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

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using COCs. The excess risk gradually disappears 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 hemorrhages. A hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal hemorrhage occur in women taking COCs.

Hepatitis C

During clinical trials with the hepatitis C virus (HCV) combination regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medicinal products such as 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.

Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol, and ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of women taking these other oestrogens, caution is warranted for co-administration with the following combination drug regimens: ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin; glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir. See section 4.5.

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 a sustained clinically significant hypertension develops during the use of a COC then it is prudent for the

physician to withdraw the COC and treat the hypertension. 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; gallstone formation; porphyria; systemic lupus erythematosus; hemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; 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 jaundice which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of COCs.

Although COCs may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics using low-dose COCs (containing <0.05 mg ethinylestradiol). However, diabetic women should be carefully observed while taking COCs, particularly in the early stage of COC use.

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

Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use (see section 4.8). Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

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

Estrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed. Patients with terminal renal insufficiency should be closely observed, since the level of circulating estrogens may be increased after administration of Qlaira.

This medicinal product contains not more than 50 mg lactose per tablet. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Medical examination/consultation

Prior to the initiation or reinstitution of Qlaira 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 Qlaira 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 for example in the following events: missed active tablets (section 4.2), gastro-intestinal disturbances (section 4.2) during active tablet taking or concomitant medication (section 4.5).

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 3 cycles.

Based on patient diaries from a comparative clinical trial, the percentage of women per cycle experiencing intracyclic bleeding was 10-18 % for women using Qlaira.

Users of Qlaira may experience amenorrhea although not being pregnant. Based on patient diaries, amenorrhea occurs in approximately 15% of cycles.

If Qlaira has been taken according to the directions described in Section 4.2, it is unlikely that the woman is pregnant. If Qlaira has not been taken according to these directions prior to the first missed withdrawal bleed or if the withdrawal bleeding is missed in two consecutive cycles, pregnancy must be ruled out before Qlaira use is continued.

If bleeding irregularities persist or occur after previously regular cycles, then non-hormonal causes should be considered and adequate diagnostic measures are indicated to exclude malignancy or pregnancy. These may include curettage.

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.

Interaction studies have only been performed in adults.

The following interactions have been reported in the literature for COCs in general or were studied in clinical trials with Qlaira.

- **Effects of other medicinal products on Qlaira**

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

Management

Enzyme induction can already be observed after a few days of treatment. Maximal enzyme induction is generally seen within a few weeks. After the cessation of drug therapy enzyme induction may be sustained for about 4 weeks.

Short-term treatment

Women on treatment with enzyme-inducing drugs should temporarily use a barrier method or another method of contraception in addition to the COC. The barrier method must be used during the whole time of the concomitant drug therapy and for 28 days after its discontinuation. If the drug therapy runs beyond the end of the active 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 HIV medication ritonavir, nevirapine and efavirenz and possibly also felbamate, griseofulvin, oxcarbazepine, topiramate and products containing the herbal remedy St. John's Wort (hypericum perforatum).

In a clinical study the strong cytochrome P450 (CYP) 3A4 inducer rifampicin led to significant decreases in steady state concentrations and systemic exposures of dienogest and estradiol. The AUC (0-24h) of dienogest and estradiol at steady state, were decreased by 83% and 44%, respectively.

Substances with variable effects on the clearance of COC:

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

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

Substances decreasing the clearance of COCs (enzyme inhibitors):

Dienogest is a substrate of CYP3A4.

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.

Coadministration with the strong CYP3A4 enzyme inhibitor ketoconazole resulted in a 2.9-fold and 1.6-fold increase of AUC (0-24h) at steady state for dienogest and estradiol, respectively. Concomitant administration of the moderate inhibitor erythromycin increased the AUC (0-24h) of dienogest and estradiol at steady state by 1.6-fold and 1.3-fold, respectively.

- **Effects of Qlaira on other medicinal products**

Oral contraceptives 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).

Pharmacokinetics of nifedipine were not affected by concomitant administration of 2 mg dienogest + 0.03 mg ethinyl estradiol thus confirming results of in vitro studies indicating that inhibition of CYP enzymes by Qlaira is unlikely at the therapeutic dose.

- **Other interactions**

Direct acting antiviral agents (DAAs) and ethinylestradiol-containing medicinal products such as CHCs

During clinical trials with the HCV combination drug regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medicinal products such as 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.

Direct acting antiviral agents (DAAs) and medicinal products containing oestrogens other than ethinylestradiol, such as estradiol

Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol, and ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of women taking these other oestrogens, caution is warranted for co-administration with the following combination drug regimens: ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin; glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir (see section 4.4).

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

Qlaira is not indicated during pregnancy.

If pregnancy occurs during use of Qlaira, further intake must be stopped. However, extensive epidemiological studies with ethinylestradiol containing COCs 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 do not indicate a risk for reproductive toxicity (see section 5.3).

The increased risk of VTE during the postpartum period should be considered when re-starting Qlaira (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. Therefore, the use of COCs should generally not be recommended until the nursing mother has completely weaned her child. Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the milk. These amounts may affect the child.

Fertility

Qlaira is indicated for the prevention of pregnancy. 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

Summary of the safety profile

The most commonly reported adverse reactions with Qlaira when used as an oral contraceptive or in the treatment of heavy menstrual bleeding in women without organic pathology who desire oral contraception are acne, breast discomfort, headache, intracyclic bleeding, nausea and weight increased.

Serious adverse reactions are arterial and venous thromboembolism, which are discussed in section 4.4.

Tabulated list of adverse reactions

The table below reports adverse reactions (ARs) by MedDRA system organ classes (MedDRA SOCs). The most appropriate MedDRA term (version 12.0) to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed, but should be taken into account as well. The frequencies are based on clinical trial data. The adverse reactions were recorded in 5 phase III clinical studies (N=2,266 women at risk for pregnancy, N=264 women suffering from dysfunctional uterine bleeding without organic pathology who desire oral contraception) and considered at least possibly causally related to Qlaira use. All ADRs listed in the category ‚rare' occurred in 1 to 2 volunteers resulting in < 0.1%.

N= 2,530 women (100.0%)

System Organ Class	**Common (≥ 1/100 to <1/10)**	**Uncommon (≥ 1/1,000 to <1/100)**	**Rare (≥ 1/10,000 to < 1/1,000)**
Infections and infestations		Fungal infection Vulvovaginal mycotic infection[1] Vaginal infection	Candidiasis Oral herpes Pelvic inflammatory disease Presumed ocular histoplasmosis syndrome Tinea versicolor Urinary tract infection Vaginitis bacterial
Metabolism and nutrition disorders		Increased appetite	Fluid retention Hypertriglyceridaemia
Psychiatric disorders		Depression/depressed mood Emotional disorder[2] Insomnia Libido decreased[3] Mental disorder Mood change[4]	Aggression Anxiety Dysphoria Libido increased Nervousness Nightmare Restlessness

			Sleep disorder Stress
Nervous system disorders	Headache[5]	Dizziness Migraine[6]	Disturbance in attention Paraesthesia Vertigo
Eye disorders			Contact lens intolerance Dry eye Eye swelling
Cardiac disorders			Myocardial infarction Palpitations
Vascular disorders		Hot flush Hypertension	Bleeding varicose vein Venous thromboembolism (VTE) Arterial thromboembolism (ATE) Hypotension Phlebitis superficialis Vein pain
Gastrointestinal disorders	Abdominal pain[7] Nausea	Diarrhoea Vomiting	Constipation Dry mouth Dyspepsia Gastrooesophageal reflux disease
Hepatobiliary disorders		Liver enzymes increased[8]	Focal nodular hyperplasia of the liver Cholecystitis chronic
Skin and subcutaneous tissue disorders	Acne[9]	Alopecia Hyperhidrosis Pruritus[10] Rash[11]	Allergic skin reaction[12] Chloasma Dermatitis Hirsutism Hypertrichosis Neurodermatitis Pigmentation disorder Seborrhoea Skin disorder[13]
Musculoskeletal and connective tissue disorders		Muscle spasms	Back pain Pain in jaw Sensation of heaviness
Renal and urinary disorders			Urinary tract pain

Reproductive system and breast disorders	Amenorrhea Breast discomfort[14] Dysmenorrhoea Intracyclic bleeding (Metrorrhagia)[15]	Breast enlargement[16] Breast mass Cervical dysplasia Dysfunctional uterine bleeding Dyspareunia Fibrocystic breast disease Menorrhagia Menstrual disorder Ovarian cyst Pelvic pain Premenstrual syndrome Uterine leiomyoma Uterine spasm Uterine/ vaginal bleeding incl. spotting[17] Vaginal discharge Vulvovaginal dryness	Abnormal withdrawal bleeding Benign breast neoplasm Breast cancer in situ Breast cyst Breast discharge Cervical polyp Cervix erythema Coital bleeding Galactorrhea Genital discharge Hypomenorrhoea Menstruation delayed Ovarian cyst ruptured Vaginal odour Vulvovaginal burning sensation Vulvovaginal discomfort
Blood and lymphatic system disorders			Lymphadenopathy
Respiratory, thoracic and mediastinal disorders			Asthma Dyspnoea Epistaxis
General disorders and administration site conditions		Fatigue Irritability Oedema[18]	Chest pain Malaise Pyrexia
Investigations	Weight increased	Weight decreased Blood pressure changes[19]	Smear cervix abnormal

[1] including vulvovaginal candidiasis and fungus cervical specimen identified
[2] including crying and affect lability
[3] including loss of libido
[4] including mood altered and mood swings
[5] including tension headache and sinus headache
[6] including migraine with aura and migraine without aura
[7] including abdominal distension, abdominal pain upper and abdominal pain lower
[8] including alanine aminotransferase increased, aspartate aminotransferase increased and gamma-glutamyltransferase increased
[9] including acne pustular
[10] including pruritus generalized and rash pruritic
[11] including rash macular
[12] including dermatitis allergic and urticaria
[13] including skin tightness
[14] including breast pain, breast tenderness, nipple disorder and nipple pain
[15] including menstruation irregular

[16] including breast swelling
[17] including vaginal hemorrhage, genital hemorrhage and uterine hemorrhage
[18] including oedema peripheral
[19] including blood pressure increased and blood pressure decreased

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.

Occurrence of amenorrhea and intracyclic bleeding based on patient diaries is summarized in section 4.4 Cycle control.

The following serious adverse events have been reported in women using COCs, which are discussed in section 4.4 Special warning and precautions for use:

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 excess number is small in relation to the overall risk of breast cancer. Causation with COC use is unknown. For further information, see sections 4.3 and 4.4;
- Liver tumours;

Other conditions

- Erythema nodosum, Erythema multiforme;
- Breast discharge;
- Hypertension;
- Occurrence or deterioration of conditions for which association with COC use is not conclusive: Crohn's disease, ulcerative colitis, epilepsy, migraine, uterine myoma, porphyria, systemic lupus erythematosus, herpes gestationis, Sydenham's chorea, haemolytic uremic syndrome, cholestatic jaundice;
- In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema;
- Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal;
- Chloasma;
- Hypersensitivity (including symptoms such as rash, urticaria);

Interactions

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal

4.9 Overdose

There have been no reports of serious deleterious effects from overdose. Symptoms that may occur in case of taking an overdose of active tablets are: nausea, vomiting and, in young girls, slight vaginal bleeding. There are no antidotes and further treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: progestogens and estrogens, sequential preparations

ATC code: G03AB08

In clinical trials performed with Qlaira in the European Union and in the USA/Canada the following Pearl indices were calculated:

Pearl Index (18-50 years of age)
Method failure: 0.42 (upper limit 95% CI 0.77)
User + method failure: 0.79 (upper limit 95% CI 1.23)

Pearl Index (18-35 years of age)
Method failure: 0.51 (upper limit 95% CI 0.97)
User + method failure: 1.01 (upper limit 95% CI 1.59)

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

In a 3-cycle ovulation inhibition study treatment with Qlaira lead to suppression of follicular development in the majority of women. Ovarian activity returned to pre-treatment levels during the post-treatment cycle.

Qlaira is dosed using an estrogen step-down and a progestin step-up regimen that can be used to treat heavy menstrual bleeding in the absence of an organic pathology, symptoms sometimes referred to as dysfunctional uterine bleeding (DUB).

Two multicenter, double blind randomised studies of similar design were performed to evaluate the efficacy and safety of Qlaira in women with symptoms of DUB who desired oral contraception. In total, 269 women were randomised on Qlaira and 152 patients on placebo.

After 6 months of treatment the median menstrual blood loss (MBL) was decreased by 88% from 142 mL to 17 mL in the Qlaira group compared to 24% from 154 mL to 117 mL in the placebo group.

After 6 months of treatment, the proportion of women who were completely cured from any DUB symptom was 29% in the Qlaira group compared to 2% in the placebo group.

The estrogen in Qlaira is estradiol valerate, an ester of the natural human 17ß-estradiol (1 mg estradiol valerate corresponds to 0.76 mg 17 ß-estradiol). This estrogen differs from the estrogens ethinylestradiol or its prodrug mestranol used in other COCs by the lack of an ethinyl group in 17alpha position.

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.

Endometrial histology was investigated in a subgroup of women (n=218) in one clinical study after 20 cycles of treatment. There were no abnormal results.

5.2 Pharmacokinetic properties

- **Dienogest**

Absorption

Orally administered dienogest is rapidly and almost completely absorbed. Maximal serum concentrations of 90.5 ng/ml are reached at about 1 hour after oral administration of the QLAIRA tablet containing 2 mg estradiol valerate + 3 mg dienogest. Bioavailability is about 91 %. The pharmacokinetics of dienogest are dose-proportional within the dose range of 1-8 mg.

Concomitant food intake has no clinically relevant effect on the rate and extent of dienogest absorption.

Distribution

A relatively high fraction of 10% of circulating dienogest is present in the free form, with approx. 90% being bound non-specifically to albumin. Dienogest does not bind to the specific transport proteins SHBG and CBG. The volume of distribution at steady state ($V_{d,ss}$) of dienogest is 46 l after the intravenous administration of 85 µg ^{3}H-dienogest.

Biotransformation

Dienogest is nearly completely metabolized by the known pathways of steroid metabolism (hydroxylation, conjugation), mainly by CYP3A4. The pharmacologically inactive metabolites are excreted rapidly resulting in dienogest as the major fraction in plasma accounting for approximately 50% of circulating dienogest derived compounds. The total clearance following the intravenous administration of ^{3}H-dienogest was calculated as 5.1 l/h.

Elimination

The plasma half-life of dienogest is approximately 11 hours. Dienogest is extensively metabolized and only 1% of drug is excreted unchanged. The ratio of urinary to fecal excretion is about 3:1 after oral administration of 0.1 mg/kg. Following oral administration, 42% of the dose is eliminated within the first 24 h and 63% within 6 days by renal excretion. A combined 86% of the dose is excreted by urine and feces after 6 days.

Steady-State Conditions

Pharmacokinetics of dienogest are not influenced by SHBG levels. Steady state is reached after 3 days of the same dosage of 3 mg dienogest in combination with 2 mg estradiol valerate. Trough, maximum and average dienogest serum concentrations at steady state are 11.8 ng/ml, 82.9 ng/ml and 33.7 ng/ml, respectively. The mean accumulation ratio for AUC (0-24h) was determined to be 1.24.

- **Estradiol valerate**

Absorption

After oral administration estradiol valerate is completely absorbed. Cleavage to estradiol and valeric acid takes place during absorption by the intestinal mucosa or in the course of the first liver passage. This gives rise to estradiol and its metabolites estrone and estriol. Maximal serum estradiol concentrations of 70.6 pg/ml are reached between 1.5 and 12 hours after single ingestion of the tablet containing 3 mg estradiol valerate on Day 1.

Biotransformation

The valeric acid undergoes very fast metabolism. After oral administration approximately 3% of the dose is directly bioavailable as estradiol. Estradiol undergoes an extensive first-pass effect and a considerable part of the dose administered is already metabolized in the gastrointestinal mucosa. Together with the presystemic metabolism in the liver, about 95 % of the orally administered dose becomes metabolized before entering the systemic circulation. The main metabolites are estrone, estrone sulfate and estrone glucuronide.

Distribution

In serum 38 % of estradiol is bound to SHBG, 60 % to albumin and 2-3 % circulate in free form. Estradiol can slightly induce the serum concentrations of SHBG in a dose-dependent manner. On day 21 of the treatment cycle, SHBG was approximately 148% of the baseline, it decreased to about 141% of the baseline by day 28 (end of placebo phase). An apparent volume of distribution of approximately 1.2 l/kg was determined after iv. administration.

Elimination

The plasma half-life of circulating estradiol is about 90 min. After oral administration, however, the situation differs. Because of the large circulating pool of estrogen sulfates and glucuronides, as well as enterohepatic recirculation, the terminal half-life of estradiol after oral administration represents a composite parameter which is dependent on all of these processes and is in the range of about 13-20 h.

Estradiol and its metabolites are mainly excreted in urine, with about 10% being excreted in the stool.

Steady-state conditions

Pharmacokinetics of estradiol are influenced by SHBG levels. In young women, the measured estradiol plasma levels are a composite of the endogenous estradiol and the estradiol generated from Qlaira. During the treatment phase of 2 mg estradiol valerate + 3 mg dienogest, maximum and average estradiol serum concentrations at steady state are 66.0 pg/ml and 51.6 pg/ml, respectively. Throughout the 28 day cycle, stable minimum estradiol concentrations were maintained and ranged from 28.7 pg/ml to 64.7 pg/ml.

Special Populations

Pharmacokinetics of Qlaira were not investigated in patients with impaired renal or liver function.

5.3 Preclinical safety data

Preclinical data reveal no special risks for humans based on conventional studies of repeated dose toxicity, genotoxicity, and toxicity to reproduction. A carcinogenicity study with dienogest in mice and a more limited study in rats showed no increase in tumours**,** however, it is well known that due to their hormonal action, sex steroids can promote the growth of certain hormone-dependent tissues and tumours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Active film-coated tablets	Placebo (inactive) film-coated tablet
Tablet core:	
Lactose monohydrate	Lactose monohydrate
Maize starch	Maize starch
Pregelatinized maize starch	Povidone K25 (E1201)
Povidone K25 (E1201)	Magnesium stearate (E572)
Magnesium stearate (E572)	
Tablet coating:	
Hypromellose type 2910 (E464)	Hypromellose type 2910 (E464)
Macrogol 6000	Talc (E553b)
Talc (E553b)	Titanium dioxide (E171)
Titanium dioxide (E171)	
Iron oxide red (E172)	
and/or	
Iron oxide yellow (E172)	

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Transparent PVC/Aluminium blister in a cardboard wallet

Presentation

Pack sizes:

1 x 28 film-coated tablets

3 x 28 film-coated tablets

6 x 28 film-coated tablets

Each wallet (28 film-coated tablets) contains in the following order: 2 dark yellow tablets and 5 medium red tablets and 17 light yellow tablets and 2 dark red tablets and 2 white tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

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A94 H2K7
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8. MARKETING AUTHORISATION NUMBER(S)

MA639/02701

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 7th January 2009

Date of Last Renewal: 1st August 2013

10. DATE OF REVISION OF THE TEXT

April 2025