

### 1.3.1.1c Summary of product characteristics (proposed clean version)

## 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: lactose (not more than 50 mg per tablet)

For a 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 embossed with the letters “DD” in a regular hexagon

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

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

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

White film-coated tablet, round with biconvex faces, one side is embossed 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.

### 4.2 Posology and method of administration

#### 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. The woman should take the last missed tablet as soon as she remembers, **even if this means taking two tablets at the same time**. She then continues to take tablets at her usual time.

Depending on the day of the cycle on which the tablet has been missed (see chart below for details), **back-up contraceptive measures** (e.g. a barrier method such as a condom) have to be used according to the following principles:

<b>DAY</b>	<b>Color</b> Content of estradiol valerate (EV)/dienogest (DNG)	<b>Principles to follow if missing <u>one</u> tablet for more than 12 hours:</b>
1 – 2	<b>Dark yellow tablets</b> (3.0 mg EV)	<ul style="list-style-type: none"> <li>- Take missed tablet immediately and the following tablet as usual (even if this means taking two tablets on the same day)</li> <li>- Continue with tablet-taking in the normal way</li> <li>- Use back-up contraception <b>for the next 9 days</b></li> </ul>
3 - 7	<b>Medium red tablets</b> (2.0 mg EV + 2.0 mg DNG)	
8 – 17	<b>Light yellow tablets</b> (2.0 mg EV + 3.0 mg DNG)	
18 – 24	<b>Light yellow tablets</b> (2.0 mg EV + 3.0 mg DNG)	<ul style="list-style-type: none"> <li>- Discard current wallet, and start immediately with the first pill of a new wallet</li> <li>- Continue with tablet-taking in the normal way</li> <li>- Back-up contraception <b>for the next 9 days</b></li> </ul>
25 – 26	<b>Dark red tablets</b> (1.0 mg EV)	<ul style="list-style-type: none"> <li>- Take missed tablet immediately and the following tablet as usual (even if this means taking two tablets on the same day)</li> <li>- No back-up contraception necessary</li> </ul>
27-28	<b>White tablets</b> (Placebos)	<ul style="list-style-type: none"> <li>- Discard missed tablet and continue tablet-taking in the normal way</li> <li>- No back-up contraception necessary</li> </ul>

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.

## Paediatric population

No data available for use in adolescents below 18 years.

## 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.

## 4.3 Contraindications

Combined oral contraceptives (COCs) should not be used in the presence of any of the conditions listed below. Should any of the conditions appear for the first time during COC use, the product should be stopped immediately.

- Venous thrombosis present or history (deep venous thrombosis, pulmonary embolism)
- Arterial thrombosis present or in history (e.g. myocardial infarction) or prodromal conditions (e.g. angina pectoris und transient ischaemic attack)
- Cerebrovascular accident present or in history
- Presence of severe or multiple risk factor(s) for venous (see 4.4) or arterial thrombosis such as:
  - diabetes mellitus with vascular symptoms
  - severe hypertension
  - severe dyslipoproteinemia
- Hereditary or acquired predisposition for venous or arterial thrombosis, such as APC-resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant).
- Pancreatitis or a history thereof if associated with severe hypertriglyceridemia.
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
- Presence or history of liver tumours (benign or malignant).
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts).
- Undiagnosed vaginal bleeding.
- History of migraine with focal neurological symptoms.
- Hypersensitivity to the active substances or to any of the excipients.

## 4.4 Special warnings and precautions for use

### Warnings

If any of the conditions/risk factors mentioned below are present, the benefits of COC use should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start taking it. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her physician. The physician should then decide whether COC use should be discontinued.

No epidemiological studies on the effects of estradiol/ estradiol valerate containing COC's exist. All the following warnings and precautions are derived from clinical and epidemiological data of *ethinyl estradiol* containing COCs. Whether these warning and precautions apply to Qlaira is unknown.

- Circulatory Disorders

Epidemiological studies have shown that the incidence of VTE in users of oral contraceptives with low oestrogen content (<50 µg ethinylestradiol) ranges from about 20 to 40 cases per 100,000 woman-years, but this risk estimate varies according to the progestogen. This compares with 5 to 10 cases per 100,000 woman-years for non-users.

The use of any combined oral contraceptive (including Qlaira) carries an increased risk of venous thromboembolism (VTE) compared with no use. The excess risk of VTE is highest during the first year a woman ever uses a combined oral contraceptive. The incidence of VTE associated with pregnancy is estimated as 60 cases per 100,000 pregnancies. VTE is fatal in 1-2% of cases.

The risk of VTE during use of Qlaira is currently unknown.

Epidemiological studies have also associated the use of ethinylestradiol containing COCs with an increased risk for arterial (myocardial infarction, transient ischaemic attack) thromboembolism.

Extremely rarely, thrombosis has been reported to occur in other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries, in COC users. There is no consensus as to whether the occurrence of these events is associated with the use of COCs.

Symptoms of venous or arterial thrombotic/thromboembolic events or of a cerebrovascular accident can include:

- unilateral leg pain and/ or swelling;
- sudden severe pain in the chest, whether or not it radiates to the left arm;
- sudden breathlessness;
- sudden onset of coughing;
- any unusual, severe, prolonged headache;
- sudden partial or complete loss of vision;

- diplopia;
- slurred speech or aphasia;
- vertigo;
- collapse with or without focal seizure;
- weakness or very marked numbness suddenly affecting one side or one part of the body; motor disturbances;
- "acute" abdomen.

The risk for venous thromboembolic events in COCs users increases with:

- increasing age
- a positive family history (venous thromboembolism ever in a sibling or parent at relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any COC use.
- prolonged immobilisation, major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue the pill (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilisation. Antithrombotic treatment should be considered if the pills have not been discontinued in advance.
- obesity (body mass index over 30 kg/m<sup>2</sup>).

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in the onset or progression of venous thrombosis.

The risk of arterial thromboembolic events or of a cerebrovascular accident increases with:

- increasing age;
- smoking (women over 35 years should be strongly advised not to smoke if they wish to use an COC);
- a positive family history (arterial thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any COC use;
- obesity (body mass index over 30 kg/m<sup>2</sup>);
- dyslipoproteinaemia;
- hypertension;
- migraine;
- valvular heart disease;
- atrial fibrillation;

The presence of one serious risk factor or multiple risk factors for venous or arterial disease, respectively, can also constitute a contra-indication. The possibility of anticoagulant therapy should also be taken into account. COC users should be specifically pointed out to contact their physician in case of possible symptoms of thrombosis. In case of suspected or confirmed thrombosis, COC use should be discontinued. Adequate alternative contraception should be initiated because of the teratogenicity of anticoagulant therapy (coumarins).

The increased risk of venous thromboembolism in the puerperium must be considered (for information on “Pregnancy and Lactation” see section 4.6).

Other medical conditions which have been associated with adverse circulatory events include diabetes mellitus, systemic lupus erythematosus, hemolytic uremic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease.

An increase in frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the COC.

- 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.

- 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.

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. 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.

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, the Lapp lactase deficiency or glucose-galactose malabsorption who are on a lactose-free diet should take this amount into consideration.

### **Medical examination/consultation**

A complete medical history (including family history) and physical examination should be taken prior to the initiation or reinstatement of COC use 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). The woman should also be instructed to carefully read the user booklet and to adhere to the advice given. The frequency and nature of examinations should be based on established practice guidelines and be adapted to the individual woman.

Women should be advised that oral contraceptives do not protect against HIV infections (AIDS) and other sexually transmitted diseases.

## Reduced efficacy

The efficacy of COCs may be reduced 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.

### • Interactions of other medicinal products on Qlaira

Interactions between oral contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. The following interactions have been reported in the literature for COCs in general or were studied in clinical trials with Qlaira.

Dienogest is a substrate of cytochrome P450 (CYP) 3A4.

Interactions can occur with phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly oxcarbazepine, topiramate, felbamate, HIV-medications (e.g. ritonavir and/or nevirapine), griseofulvin and the herbal remedy St. John's wort (*hypericum perforatum*). The mechanism of this interaction appears to be based on the hepatic enzyme-inducing properties (e.g. CYP 3A4 enzymes) of these drugs which can result in increased clearance of sex hormones.

Maximal enzyme induction is generally not seen for 2-3 weeks but may then be sustained for at least 4 weeks after the cessation of drug therapy.

In a clinical study the strong 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.

Women on short-term treatment (up to one week) with any of the above-mentioned classes of medicinal products or individual active substances besides rifampicin should temporarily use a barrier method in addition to the COC, i.e. during the time of concomitant medicinal product administration and for 14 days after their discontinuation.

For women on rifampicin a barrier method should be used in addition to the COC during the time of rifampicin administration and for 28 days after its discontinuation.

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

Known CYP3A4 enzyme inhibitors like azole antifungals, cimetidine, verapamil, macrolides, diltiazem, antidepressants and grapefruit juice may increase plasma levels of dienogest.

In a clinical study investigating the effect of CYP3A4 inhibitors (ketoconazole, erythromycin), steady state dienogest and estradiol plasma levels were increased. Co-administration with the strong CYP3A4 enzyme inhibitor ketoconazole resulted in a 186% and 57% 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 62% and 33%, respectively. The clinical relevance of these interactions is unknown.

Contraceptive failures have also been reported with antibiotics, such as penicillins and tetracyclines. The mechanism of this effect has not been elucidated.

- **Interactions 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.

- **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 Pregnancy and lactation**

Qlaira should not be used during pregnancy.

If pregnancy occurs during use of Qlaira, further intake should 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).

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.

#### **4.7 Effects on ability to drive and use machines**

Qlaira has no influence on the ability to drive or use machines.

#### **4.8 Undesirable effects**

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%)

<b>System Organ Class</b>	<b>Common (≥ 1/100 to 1/10)</b>	<b>Uncommon (≥ 1/1,000 to &lt;1/100)</b>	<b>Rare (≥ 1/10,000 to &lt; 1/1,000)</b>
Infections and infestations		Fungal infection Vulvovaginal mycotic infection <sup>1</sup> 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 <sup>2</sup> Insomnia Libido decreased <sup>3</sup> Mental disorder Mood change <sup>4</sup>	Aggression Anxiety Dysphoria Libido increased Nervousness Nightmare Restlessness Sleep disorder Stress
Nervous system disorders	Headache <sup>5</sup>	Dizziness Migraine <sup>6</sup>	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 Hypotension Phlebitis superficialis Vein pain
Gastrointestinal disorders	Abdominal pain <sup>7</sup> Nausea	Diarrhoea Vomiting	Constipation Dry mouth Dyspepsia Gastrooesophageal reflux disease
Hepatobiliary disorders		Liver enzymes increased <sup>8</sup>	Focal nodular hyperplasia of the liver Cholecystitis chronic
Skin and subcutaneous tissue disorders	Acne <sup>9</sup>	Alopecia Hyperhidrosis Pruritus <sup>10</sup> Rash <sup>11</sup>	Allergic skin reaction <sup>12</sup> Chloasma Dermatitis Hirsutism Hypertrichosis Neurodermatitis Pigmentation disorder Seborrhoea Skin disorder <sup>13</sup>
Musculoskeletal and connective tissue disorders		Muscle spasms	Back pain Pain in jaw Sensation of heaviness
Renal and urinary disorders			Urinary tract pain

<b>System Organ Class</b>	<b>Common (≥ 1/100 to 1/10)</b>	<b>Uncommon (≥ 1/1,000 to &lt;1/100)</b>	<b>Rare (≥ 1/10,000 to &lt; 1/1,000)</b>
Reproductive system and breast disorders	Amenorrhea Breast discomfort <sup>14</sup> Dysmenorrhoea Intracyclic bleeding (Metrorrhagia) <sup>15</sup>	Breast enlargement <sup>16</sup> 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 <sup>17</sup> 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 <sup>18</sup>	Chest pain Malaise Pyrexia
Investigations	Weight increased	Weight decreased Blood pressure changes <sup>19</sup>	Smear cervix abnormal

<sup>1</sup> including vulvovaginal candidiasis and fungus cervical specimen identified

<sup>2</sup> including crying and affect lability

<sup>3</sup> including loss of libido

<sup>4</sup> including mood altered and mood swings

<sup>5</sup> including tension headache and sinus headache

<sup>6</sup> including migraine with aura and migraine without aura

<sup>7</sup> including abdominal distension, abdominal pain upper and abdominal pain lower

<sup>8</sup> including alanine aminotransferase increased, aspartate aminotransferase increased and gamma-glutamyltransferase increased

<sup>9</sup> including acne pustular

<sup>10</sup> including pruritus generalized and rash pruritic

<sup>11</sup> including rash macular

<sup>12</sup> including dermatitis allergic and urticaria

<sup>13</sup> including skin tightness

<sup>14</sup> including breast pain, breast tenderness, nipple disorder and nipple pain

<sup>15</sup> including menstruation irregular

<sup>16</sup> including breast swelling

<sup>17</sup> including vaginal hemorrhage, genital hemorrhage and uterine hemorrhage

<sup>18</sup> including oedema peripheral

<sup>19</sup> including blood pressure increased and blood pressure decreased

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:

- Venous thromboembolic disorders;
- Arterial thromboembolic disorders;
- Hypertension;
- Liver tumours;
- 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;
- Chloasma;
- Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal.
- In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema.

The frequency of diagnosis of breast cancer is very slightly increased among OC users. As breast cancer is rare in women under 40 years of age the excess number is small in relation to the overall risk of breast cancer. Causation with COC use is unknown. For further information, see sections 4.3 and 4.4.

In addition to the above mentioned adverse reactions, erythema nodosum, erythema multiforme, breast discharge and hypersensitivity have occurred under treatment with ethinylestradiol containing COCs. Although these symptoms were not reported during the clinical studies performed with Qlaira, the possibility that they also occur under treatment cannot be ruled out.

## **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: G03AB

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.

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 17 $\beta$ -estradiol (1 mg estradiol valerate corresponds to 0.76 mg 17  $\beta$ -estradiol). This estrogen differs from the estrogens ethinylestradiol or its prodrug mestranol used in other COCs by the lack of an ethinyl group in 17 $\alpha$  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 QLAIIRA 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  $\mu\text{g}$   $^3\text{H}$ -dienogest.

### Metabolism

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  $^3\text{H}$ -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.

### **Metabolism**

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

<u>Active film-coated tablets</u>	<u>Placebo (inactive) film-coated tablet</u>
	<i>Tablet core:</i>
Lactose monohydrate	Lactose monohydrate
Maize starch	Maize starch
Pregelatinized maize starch	Povidone K25 (E1201)
Povidone K25 (E1201)	Magnesium stearate (E572)
Magnesium stearate (E572)	
	<i>Tablet coating:</i>
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**

## **8. MARKETING AUTHORISATION NUMBER(S)**

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

## **10. DATE OF REVISION OF THE TEXT**