NEW ZEALAND DATA SHEET

1. PRODUCT NAME

QLAIRA® 3 mg; 2 mg / 2 mg; 2 mg / 3 mg; 1 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dark yellow tablet contains: 3 mg estradiol valerate

Each medium red tablet contains: 2 mg estradiol valerate and 2 mg dienogest

Each light yellow tablet contains: 2 mg estradiol valerate and 3 mg dienogest

Each dark red tablet contains: 1 mg estradiol valerate

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

QLAIRA active tablets have 4 presentations: dark yellow film coated tablets, medium red film coated tablets, light yellow film coated tablets and dark red film coated tablets.

QLAIRA placebo tablets are white film coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of heavy and/or prolonged menstrual bleeding in women without organic pathology who desire oral contraception.

4.2 Dose and method of administration

Combined oral contraceptives (COCs), when taken correctly, have a failure rate of approximately 1% per year. The failure rate may increase when pills are missed or taken incorrectly.

Treatment of heavy and/or prolonged menstrual bleeding with QLAIRA has been shown to result in a rapid normalisation of excessive menstrual blood losses. If QLAIRA has been taken according to the directions provided under “How to take QLAIRA” and the patient does not experience a reduction of her menstrual bleeding after 3 treatment cycles then treatment with QLAIRA should be ceased and other treatment options should be considered.

How to take QLAIRA

Tablets must be taken in the order directed on the wallet pack 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). If QLAIRA is taken in this manner, the woman is protected against pregnancy immediately.

- **Changing from a combined hormonal contraceptive or vaginal ring**

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 has been used, the woman should start taking QLAIRA on the day of removal.

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

The woman may switch any day from the minipill (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 need not take additional contraceptive measures.

- **Following delivery or second-trimester abortion**

For breastfeeding women see Section 4.4 Special warnings and precautions for use.

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 active 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 active tablet, contraceptive protection may be reduced.

Depending on the day of the cycle 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	**Colour** Content of estradiol	**Principles to follow if missing *one* tablet for more than 12 hours:**

	valerate (EV) / dienogest (DNG)	
1-2	**Dark yellow tablets** (3.0mg EV)	- Take the missed tablet immediately - Take the next tablet at the same time as usual (even if this means taking two tablets on 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** (2.0mg EV + 2.0mg DNG)	
8-17	**Light yellow tablets** (2.0mg EV + 3.0mg DNG)	
18-24	**Light yellow tablets** (2.0mg EV + 3.0mg 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** (1.0mg EV)	- Take the missed tablet immediately - Take the next tablet at the same time as usual (even if this means taking two tablets on the same day) - Continue taking one tablet each day at the same time as usual - No back-up contraception necessary
27-28	**White tablets** (Placebo)	- Discard the missed tablet - Take the next tablet 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.

Paediatric population

There is no relevant indication for use of QLAIRA (in children) before menarche.

Advice in case of gastrointestinal disturbances

In case of severe gastrointestinal disturbances, absorption may not be complete and additional contraceptive measures should be taken.

If vomiting occurs within 3-4 hours after active tablet-taking, the advice concerning missed tablets is applicable (see section Management of missed tablets). If the woman does not want to change her normal tablet-taking schedule, she has to take the extra 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.

- Presence or risk of venous thromboembolism (VTE) (see 4.4 Special warnings and precautions for use)
  - Current VTE (on anticoagulants) or history of 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
  - A high risk of venous thromboembolism due to the presence of multiple risk factors
- Presence or risk of arterial thromboembolism (ATE) (see 4.4 Special warnings and precautions for use)
  - Current ATE or history of ATE (e.g. myocardial infarction or stroke) or prodromal condition (e.g. angina pectoris or transient ischaemic attack [TIA])
  - Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (eg. anticardiolipin-antibodies and lupus anticoagulant)
  - History of migraine with focal neurological symptoms
  - A high risk of arterial thromboembolism due to multiple risk factors or to the presence of one serious risk factor such as:
    - diabetes mellitus with vascular symptoms
    - severe hypertension
    - severe dyslipoproteinaemia
- 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
- Known or suspected pregnancy
- Hypersensitivity to any of the ingredients contained in QLAIRA.

4.4 Special warnings and precautions for use

If any of the conditions / risk factors mentioned below are present, the benefits of QLAIRA 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 doctor. The doctor should then decide whether QLAIRA should be discontinued.

QLAIRA is indicated for treatment of heavy and/or prolonged menstrual bleeding only in women without organic pathology.

The following warnings and precautions are mainly derived from clinical and epidemiological data of ethinylestradiol-containing combined oral contraceptives (COCs)

Circulatory Disorders

Epidemiological studies have suggested an association between the use of ethinylestradiol containing COCs and an increased risk of arterial and venous thrombotic and

thromboembolic diseases such as myocardial infarction, stroke, deep venous thrombosis, and pulmonary embolism. These events occur rarely in average-risk women.

Risk of venous thromboembolism (VTE)

The use of any COC increases the risk of VTE compared with no use. The woman should be advised that her VTE risk is highest in the first ever year of use and that there is some evidence that the risk is increased when a COC is re-started after a break in use of 4 weeks or more.

Data from a large, prospective 3-armed cohort study[1,2] suggest that this increased risk is mainly present during the first 3 months.

Overall the risk for VTE in users of low estrogen dose (< 50 µg ethinylestradiol) COCs is two to three fold higher than for non-users of COCs who are not pregnant and remains lower than the risk associated with pregnancy and delivery.

VTE, manifesting as DVT and/or PE, may occur during the use of all COCs. A large, prospective 3-armed cohort study[1] has shown that the frequency of VTE diagnosis ranges between 8 to 10 per 10,000 woman years in low estrogen dose (<50 µg ethinylestradiol) COC users. The most recent data suggest that the frequency of VTE diagnosis is approximately 4.4 per 10,000 woman years in non-pregnant non-COC users[1], and ranges between 20 to 30 per 10,000 pregnant women or post partum.[1,3]

One post approval commitment study has been completed specifically for QLAIRA. In this prospective active surveillance study, the incidence of VTE in women with or without other risk factors for VTE who used QLAIRA is in the same range as that for users of levonorgestrel-containing COCs.

It is important that women understand that VTE associated with COC use is rare in average-risk women. The risk in pregnancy (5-20 per 10,000 women over 9 months) and the risk in the post-partum period (45-65 per 10,000 women over 12 weeks) is higher than that as associated with COC use.

An additional increase in VTE risk for COCs containing ≥ 50 µg ethinylestradiol cannot be excluded.

The decision to use any product other than one with the lowest VTE risk should be taken only after a discussion with the woman to ensure she understands the risk of VTE with COCs, and how her current risk factors influence this risk.

The increased risk of VTE during the postpartum period must be considered if re-starting QLAIRA. See 4.2 Dose and method of administration, 4.6 Fertility, pregnancy and lactation.

VTE may be life-threatening or may have a fatal outcome (in 1-2% of cases).

Extremely rarely, thrombosis has been reported to occur in COC users in other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries.

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[1] Dinger JC, Heinemann LAJ, Kuhl-Habich D. The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance study on Oral Contraceptives based on 142,475 women-years of observation. Contraception 2007;75:344-354.

[2] Long-term Active Surveillance Study for Oral Contraceptives (LASS), 2nd update report based on study status of May 2009.

[3] Heit J A et al. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30 year population-based study. Annals of Internal Medicine:2005;143/10:697-708.

The risk for venous thromboembolic complications in COC users may increase substantially in a woman with additional risk factors, particularly if there are multiple risk factors (see list below).

QLAIRA is contraindicated if a woman has multiple risk factors that put her at high risk of venous thrombosis. 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 COC should not be prescribed.

When considering risk/benefit, the doctor should take into account that the adequate treatment of a condition may reduce the associated risk of thrombosis.

Risk factors for VTE

- Obesity (body mass index over 30 kg/m²). Risk increases substantially as BMI rises
- Prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma
- Temporary immobilisation including air travel >4 hours can also be a risk factor for VTE, particularly in women with other risk factors
- Positive family history (venous thromboembolism ever in a sibling or parent especially at a relatively early age e.g. before 50)
- Biochemical factors that may be indicative of hereditary or acquired predisposition for VTE include Activated Protein C (APC) resistance (including Factor V Leiden), antithrombin-III deficiency, protein C deficiency, protein S deficiency
- Other medical conditions associated with VTE include:
  - Cancer
  - Systemic lupus erythematosus
  - Haemolytic uraemic syndrome
  - Chronic inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis)
  - Sickle cell disease
- Increasing age, particularly above 35 years
- Smoking

In women at risk of prolonged immobilisation (including major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma), it is advisable to discontinue use of QLAIRA (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.

If a hereditary predisposition to VTE is suspected, the woman should be referred to a specialist for advice before deciding about any COC use.

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in venous thromboembolism.

Symptoms of VTE (DVT and PE)

Women should be informed of the symptoms of VTE and be advised to seek urgent medical attention if VTE symptoms develop and to inform the healthcare professional that she is taking a COC.

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 or sudden severe pain in the chest which may increase with deep breathing
- 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 COCs with an increased risk for arterial thromboembolism (e.g. myocardial infarction, angina pectoris, stroke or TIA). Arterial thromboembolic events may be fatal.

The risk of arterial thromboembolic complications in COC users increases in women with risk factors. QLAIRA is contraindicated if a woman has one serious or multiple risk factors for ATE that puts her at high risk of arterial thrombosis. 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 COC should not be prescribed.

<u>Risk factors for ATE</u>
- Increasing age, particularly above 35 years
- Smoking
- Hypertension
- Obesity
- Positive family history (arterial thromboembolism ever in a sibling or parent especially at relatively early age e.g. below 50).
- Biochemical factors that may be indicative of hereditary or acquired predisposition for ATE include: hyperhomocysteinaemia and antiphospholipid antibodies (e.g. anticardiolipin antibodies, and lupus anticoagulant).
- Migraine
- Other medical conditions associated with adverse vascular events:
  - Diabetes mellitus
  - Hyperhomocysteinaemia
  - Valvular heart disease
  - Atrial fibrillation
  - Dyslipoproteinaemia
  - Systemic lupus erythematosus

Women should be advised not to smoke if they wish to use a COC. Women over 35 years who continue to smoke should be strongly advised to use a different method of contraception.

If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any COC use.

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.

Symptoms of ATE

Women should be informed of the symptoms of ATE and be advised to seek urgent medical attention if ATE symptoms develop and to inform the healthcare professional that she is taking a COC.

Symptoms of a stroke 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, slurred speech or aphasia
- sudden partial or complete loss of vision; diplopia
- 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

Other conditions

Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when taking 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 doctor 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; haemolytic 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 of a need to alter the therapeutic regimen in diabetics taking low-dose COCs (containing < 0.05 mg ethinylestradiol). However, diabetic women should be carefully observed while taking COCs.

Crohn's disease and ulcerative colitis have been associated with COC use.

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

Each dark yellow, medium red, light yellow or dark red active film-coated tablet contains 46 mg, 45 mg, 48 mg or 44 mg of lactose per tablet, respectively. Each placebo white film-coated tablet contains 50 mg of lactose. 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 and physical examination should be taken prior to the initiation or reinstitution of COC use, guided by the contraindications and precautions, and should be repeated periodically. Periodic medical assessment is also of importance because contraindications (e.g. a transient ischaemic attack) or risk factors (e.g. a family history of venous or arterial thrombosis) may appear for the first time during the use of a COC. The frequency and nature of these assessments should be based on established practice guidelines and be adapted to the individual woman but should generally include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology.

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

Reduced efficacy

The efficacy of COCs may be reduced for example in the following events: missed active tablets (see 4.2 Dose and method of administration - Management of missed tablets), gastrointestinal disturbances during active tablet taking (see 4.2 Dose and method of administration - Advice in case of gastrointestinal disturbances) or concomitant medication (see 4.5 Interaction with other medicines and other forms of interaction).

Cycle control

Analyses of bleeding patterns and cycle control demonstrated that bleeding patterns were comparable to those of low-dose COCs, whereas the cycle control was characterised by absence of withdrawal bleeding in more cases (range: 16.8% to 22.3%) than observed with the comparator (range: 6.2% to 10.5%).

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.

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

In some women withdrawal bleeding may not occur during the placebo tablet phase. If the COC has been taken according to the directions described in dosage and administration, it is unlikely that the woman is pregnant. However, if the COC has not been taken according to these directions prior to the first missed withdrawal bleed or if two withdrawal bleeds are missed, pregnancy must be ruled out before COC use is continued.

Patients with hepatic impairment

QLAIRA is contraindicated in women with severe hepatic diseases whilst liver function values have not returned to normal (see also 4.3 Contraindications).

Patients with renal impairment

QLAIRA has not been specifically studied in renally impaired patients. Available data do not suggest a change in treatment in this patient population.

Use in the elderly

Not applicable. QLAIRA is not indicated after menopause.

Paediatric use

QLAIRA is only indicated after menarche.

Effects on 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.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicinal products on QLAIRA

Interactions can occur with medicine that induce microsomal enzymes (e.g. cytochrome P450 CYP3A4 enzyme) which can result in increased clearance of sex hormones and which may lead to breakthrough bleeding and/or contraceptive failure.

Women receiving treatment with any of these medicines should temporarily use a barrier method in addition to the COC or choose another method of contraception. The barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation.

- **Substances increasing the clearance of COCs (diminished efficacy of COCs by enzyme-induction) e.g.:**

*P*henytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St. John's Wort (*hypericum perforatum*).

The effect of CYP 3A4 inducer rifampicin was studied in healthy postmenopausal women. Co-administration of rifampicin with estradiol valerate/dienogest tablets led to significant decreases in steady state concentrations and systemic exposures of dienogest and estradiol. The systemic exposure of dienogest and estradiol at steady state, measured by AUC (0-24h), were decreased by 83% and 44%, respectively.

- **Substances with variable effects on the clearance of COCs, e.g.:**

When co-administered with COCs, many human immunodeficiency virus (HIV)/hepatitis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of estrogen or progestogen. These changes may be clinically relevant in some cases.

- **Antibiotics (interference with enterohepatic circulation):**

Some clinical reports suggest that enterohepatic circulation of estrogens may decrease when certain antibiotic agents are given, which may reduce estradiol concentrations (e.g. penicillins, tetracyclines).

- **Substances decreasing the clearance of COCs (enzyme inhibitors)**

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

Strong and moderate CYP 3A4 inhibitors such as azole antifungals (e.g. ketoconazole, itraconazole, voriconazole, fluconazole), cimetidine, verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem, antidepressants and grapefruit juice can increase plasma levels of the estrogen or the progestogen or both.

In a study investigating the effect of CYP 3A4 inhibitors (ketoconazole, erythromycin), steady state dienogest and estradiol plasma levels were increased. Co-administration with the strong inhibitor ketoconazole resulted in a 186% increase of AUC (0-24h) at steady state for dienogest and a 57% increase for estradiol. When co-administered with the moderate inhibitor erythromycin, the AUC (0-24h) of dienogest and estradiol at steady state were increased by 62% and 33%, respectively.

Effects of QLAIRA on other medicinal products

Oral contraceptives may affect the metabolism of certain other medicines. Accordingly, plasma and tissue concentrations may either increase or decrease (e.g. lamotrigine). However, based on the *in vitro* data, inhibition of CYP enzymes by QLAIRA is unlikely at the therapeutic dose. Note: The product information of concomitant medications should be consulted to identify potential interactions.

4.6 Fertility, pregnancy and lactation

Effects on Fertility

QLAIRA is indicated for prevention of pregnancy.

Use in pregnancy (Category B34)

QLAIRA is contraindicated in 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 early pregnancy.

The reproductive toxicity of QLAIRA has not been assessed in animals. However, studies have been performed for 17β-estradiol and dienogest, the active components of QLAIRA.

Oral treatment of rats and rabbits with dienogest during organogenesis caused an increase in postimplantation loss at systemic exposure levels (based on AUC) less than that anticipated clinically. No teratogenicity was evident in either species at systemic exposure levels up to around 8- (rat) or 15- (rabbit) fold higher than that expected at the clinical dose. Oral treatment of rats with dienogest during late pregnancy and lactation was shown to impair fertility in the offspring at maternal systemic exposure levels (based on AUC) considerably less than that anticipated clinically.

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[4] **Category B3**
Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Use in lactation

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

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Undesirable effects

The most serious undesirable effects associated with the use of COCs are described under 4.4 Special warnings and precautions for use.

Oral contraception

Table 1 below reports adverse drug reactions (ADRs) by MedDRA system organ classes (MedDRA SOCs). The most appropriate MedDRA term (version 10.0) 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 drug reactions were recorded in 3 phase III clinical studies (N=2266 women at risk for pregnancy) and considered at least possibly causally related to QLAIRA use. All ADRs listed in the category ‘rare’ occurred in 1 to 2 patients resulting in < 0.1%.

Table 1: Adverse drug reactions, phase III clinical trials, N=2266 women (100%)

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 Vaginal candidiasis Vaginal infection	Candidiasis Herpes simplex Presumed ocular histoplasmosis syndrome Tinea versicolor Urinary tract infection

System Organ Class	Common (≥ 1/100 to <1/10)	Uncommon (≥ 1/1,000 to <1/100)	Rare (≥ 1/10,000 to < 1/1,000)
			Vaginitis bacterial Vulvovaginal mycotic infection
Metabolism and nutrition disorders		Increased appetite	Fluid retention Hypertriglyceridaemia
Psychiatric disorders		Depression/depressed mood Libido decreased Mental disorder Mood change	Affect lability Aggression Anxiety Dysphoria Libido increased Nervousness Restlessness Sleep disorder Stress
Nervous system disorders	Headache (including tension headache)	Dizziness	Disturbance in attention Paraesthesia Vertigo
Eye disorders			Contact lens intolerance
Vascular disorders		Hypertension Migraine (including migraine with aura and migraine without aura)	Bleeding varicose vein Hot flush Hypotension Vein pain
Gastrointestinal disorders	Abdominal pain (including abdominal distension)	Diarrhoea Nausea Vomiting	Constipation Dyspepsia Gastrooesophageal reflux disease
Hepatobiliary disorders			Alanine aminotransferase increased Focal nodular hyperplasia of the liver
Skin and subcutaneous tissue disorders	Acne	Alopecia Pruritus (including pruritus generalised and rash pruritic) Rash (including rash macular)	Allergic skin reaction (including dermatitis allergic and urticaria) Chloasma Dermatitis Hirsutism Hypertrichosis Neurodermatitis Pigmentation disorder Seborrhoea Skin disorder (including skin tightness)
Musculoskeletal and connective tissue disorders			Back pain Muscle spasms Sensation of heaviness
Reproductive system and breast disorders	Amenorrhea Breast discomfort (including breast pain,	Breast enlargement Breast mass Cervical dysplasia	Benign breast neoplasm Breast cyst Coital bleeding

System Organ Class	Common (≥ 1/100 to <1/10)	Uncommon (≥ 1/1,000 to <1/100)	Rare (≥ 1/10,000 to < 1/1,000)
	nipple disorder and nipple pain) Dysmenorrhoea Intracyclic bleeding (Metrorrhagia) (including menstruation irregular)	Dysfunctional uterine bleeding Dyspareunia Fibrocystic breast disease Menorrhagia Menstrual disorder Ovarian cyst Pelvic pain Premenstrual syndrome Uterine leiomyoma Uterine spasm Vaginal discharge Vulvovaginal dryness	Galactorrhoea Genital haemorrhage Hypomenorrhoea Menstruation delayed Ovarian cyst ruptured Vaginal burning sensation Uterine/vaginal bleeding incl. spotting Vaginal odour Vulvovaginal discomfort
Blood and lymphatic system disorders			Lymphadenopathy
General disorders and administration site conditions		Irritability Oedema	Chest pain Fatigue Malaise
Investigations	Weight increased	Weight decreased	

The comparative rates for adverse reactions for treatment (N=399) in comparison to the reference COC containing 0.02 mg EE and 0.10 mg levonorgestrel (N=399) in study 304004/A35644 were: breast pain (3.3% vs. 1.0%), headache (1.8% vs. 1.8%), acne (1.3% vs. 2.3%), alopecia (0.8% vs. 1.0%), migraine (0.5% vs. 1.3%) and weight increased (0.5% vs. 1.0%).

Treatment of heavy and/or prolonged menstrual bleeding in women without organic pathology who desire oral contraception

Table 2 below reports adverse drug reactions (ADRs) by MedDRA system organ classes (MedDRA SOCs). The frequencies are based on clinical trial data. The adverse drug reactions were recorded in 2 phase III clinical studies (N=264 women suffering from heavy and/or prolonged bleeding without organic pathology who desire oral contraception) and considered at least possibly causally related to QLAIRA use.

Table 2: Adverse drug reactions, phase III clinical trials, N=264 women (100%)

System Organ Class	Common (≥ 1/100 to <1/10)	Uncommon (≥ 1/1,000 to <1/100)
Infections and infestations	Vulvovaginal mycotic infection (including vaginal cadidiasis)	Pelvic inflammatory disease
Metabolism and nutrition disorders		Fluid retention Increased appetite
Psychiatric disorders	Emotional disorder (including affect lability and crying) Insomnia Libido decreased Mood changes	Depression/depressed mood Nightmare

System Organ Class	Common (≥ 1/100 to <1/10)	Uncommon (≥ 1/1,000 to <1/100)
Nervous system disorders	Headache (including tension headache and sinus headache) Migraine (including migraine with aura)	
Eye disorders		Dry eye Eye swelling
Cardiac disorders		Myocardial infarction Palpitations
Vascular disorders		Hot flush Hypertension Phlebitis superficialis Vein pain
Gastrointestinal disorders	Abdominal pain (including abdominal distension and abdominal pain lower) Nausea	Constipation Dry mouth Vomiting
Hepatobiliary disorders	Liver enzymes increased (including alanine aminotransferase increased, aspartate aminotransferase increased and gamma-glutamyltransferase increased)	Cholecystitis chronic
Skin and subcutaneous tissue disorders	Acne	Alopecia Hirsurtism Hyperhidrosis Pruritus generalised Rash
Musculoskeletal and connective tissue disorders		Muscle spasms Pain in jaw
Neoplasms benign, malignant and unspecified (including cysts and polyps)		Breast cancer in situ
Renal and urinary disorders		Urinary tract pain
Reproductive system and breast disorders	Breast discomfort (including breast pain and breast tenderness) Dysmenorrhea Genital discharge Menorrhagia Intracyclic bleeding (metrorrhagia) (including withdrawal bleeding irregular) Uterine/vaginal bleeding including spotting (including genital haemorrhage and uterine haemorrhage)	Breast discharge Breast enlargement Cervical polyp Cervix erythema Fibrocystic breast disease Menstrual disorder Ovarian cyst Pelvic pain Premenstrual syndrome Vulvovaginal dryness
Respiratory, thoracic and mediastinal disorders		Asthma Dyspnoea Epistaxis

System Organ Class	Common (≥ 1/100 to <1/10)	Uncommon (≥ 1/1,000 to <1/100)
General disorders and administration site conditions	Fatigue	Oedema peripheral Pyrexia
Investigations	Blood pressure changes (including blood pressure increased and blood pressure decreased) Weight increased	Smear cervix abnormal

In addition to the above mentioned adverse reactions, erythema nodosum, erythema multiforme, breast discharge and hypersensitivity have occurred under treatment with ethinyl estradiol 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.

In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

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. In cases of overdose, it is advisable to contact the Poisons Information Centre (New Zealand: 0800 POISON or 0800 764 766) for recommendations on the management and treatment of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacodynamic effects

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 and the changes in cervical secretions. As well as protection against pregnancy, COCs have several positive properties which, next to the negative properties (see 4.4 Special warnings and precautions for use, 4.8 Undesirable effects), can be useful in deciding on the method of birth control. The cycle is more regular, menstruation is often less painful and bleeding is lighter. The latter may result in a decrease in the occurrence of iron deficiency. In addition, there is evidence of a reduced risk of endometrial cancer and ovarian cancer. The higher dosed COCs (0.05 mg ethinylestradiol) have been shown to reduce the incidence of ovarian cysts, pelvic inflammatory disease, benign breast disease and ectopic pregnancy. Whether this also applies to estradiol valerate containing COCs remains to be confirmed.

The estrogen in QLAIRA is estradiol valerate, a prodrug of the natural human 17β-estradiol. The estrogenic component used in this COC is therefore different from the estrogens usually used in COCs which are the synthetic estrogens ethinylestradiol or its prodrug mestranol both containing an ethinyl group in the 17 alpha position.

QLAIRA leads to lower hepatic effects when compared to a triphasic ethinylestradiol/levonorgestrel (EE/LNG)-containing COC. The impact on sex hormone binding globulin (SHBG) levels and haemostasis parameters was shown to be lower. In combination with dienogest, estradiol valerate displays an increase in HDL, while LDL-cholesterol levels are slightly decreased.

Dienogest is an orally and parenterally potent progestogen which has additional antiandrogenic partial effects. Its estrogenic, antiestrogenic and androgenic properties are negligible. As a result of the special chemical structure, a pharmacological spectrum of action is obtained which combines the most important advantages of the 19-nor progestogens and of the progesterone derivatives. Endometrial histology was investigated in a small subgroup of women in one clinical study after 20 cycles of treatment. There were no abnormal results. Findings were in accordance with the typical endometrial changes described for EE containing COCs.

Clinical efficacy and safety

Oral contraception

The contraceptive efficacy and safety of QLAIRA was examined in three multicenter phase III studies that included healthy women aged 18 to 50 years requesting contraception. The contraceptive reliability was analysed using 2 different methods, the PI (Pearl Index) and a life table analysis.

The first of these studies, the pivotal Pearl Index study 306660/A35179, was an open, uncontrolled, one-arm study to evaluate the contraceptive efficacy and the safety of estradiol valerate/dienogest (QLAIRA) for 20 cycles. The PI served as primary criterion for the assessment of contraceptive reliability. The PI_U (unadjusted Pearl Index) was 0.7257 with an upper limit of the two-sided 95% CI of 1.2410 based on 13 pregnancies considered as having occurred during treatment in the entire study population of women aged 18 to 50 years. Six pregnancies assessed as method failure were taken into account for the calculation of the PI_A (adjusted Pearl Index). The PI_A was 0.3370 with an upper limit of the two-sided 95% CI of 0.7335.

The second study (304004/A35644) was pivotal with regard to bleeding patterns and cycle control and was a double-blind, double-dummy, controlled, randomised study to evaluate bleeding patterns, cycle control, and safety of QLAIRA in comparison to a reference COC containing 0.02 mg EE and 0.10 mg levonorgestrel, over a treatment period of 7 cycles. Only 1 pregnancy occurred during the treatment phase of the study. This occurred in the comparator group and was assessed as method failure.

The third study (304742/A39818) was an open, uncontrolled, one-arm study to evaluate the contraceptive efficacy, cycle control, safety and tolerability of QLAIRA over a period of 13 treatment cycles, which was extended to a maximum of 28 cycles. The primary efficacy variable was the number of observed pregnancies i.e. unintended pregnancy during study treatment. Of the 6 confirmed pregnancies that occurred during treatment, 4 pregnancies were considered as method failures and 2 pregnancies as subject failures.

The analysis of the pooled data from the three efficacy studies described above supported the contraceptive reliability of QLAIRA: the PI_U in women aged 18 to 50 years was 0.7878,

with an upper limit of the two-sided 95% CI of 1.2302. The PI_A calculated on the basis of 10 pregnancies rated as method failure was 0.4193, with an upper two-sided 95% CI of 0.7711. Compliance was high throughout these studies.

As a decrease in fertility in women beyond 35 is known, a separate PI calculation was presented for the younger age group of women (18 to 35 years). In the subgroup of women aged 18 to 35 years, there were 18 pregnancies considered as having occurred during treatment. The corresponding PI_U was 1.0064 and the upper limit of the two-sided 95% CI was 1.5906. There were 9 pregnancies assessed as method failure. The corresponding PI_A was 0.5102 and the upper limit of the two-sided 95% CI was 0.9685.

In addition to the calculation of the PI, a life table analysis was performed for the time up to the occurrence of a pregnancy. The cumulative failure rate, i.e. the probability of becoming pregnant, was calculated using the Kaplan-Meier estimator on the basis of unintended pregnancies considered to have occurred during treatment. In the first study, the Kaplan Meier estimate for the cumulative failure rate over an exposure time to the study drug of 545 days was 0.0109 (95% CI = 0.0063 to 0.0188) in 18 to 50 year old women and 0.0142 (95% CI = 0.0080 to 0.0251) in 18 to 35 year old women. The Kaplan-Meier estimate for the cumulative failure rate over an exposure time to the study drug of 545 days based on pooled data from the three studies was 0.0117 (95% CI = 0.0074 to 0.0186) for women 18 to 50 years of age and 0.0152 (95% CI = 0.0094 to 0.0243) in the subgroup of women 18 to 35 years of age. These findings are in line with a failure rate of approximately 1% per year for COCs when correctly taken.

The majority of women were satisfied with the study medication and compliance was high.

The safety profile of QLAIRA was not different from that of established low-dose COCs even though a considerable number of women older than 35 years of age were included in the clinical studies.

Treatment of heavy and/or prolonged menstrual bleeding in women without organic pathology who desire oral contraception

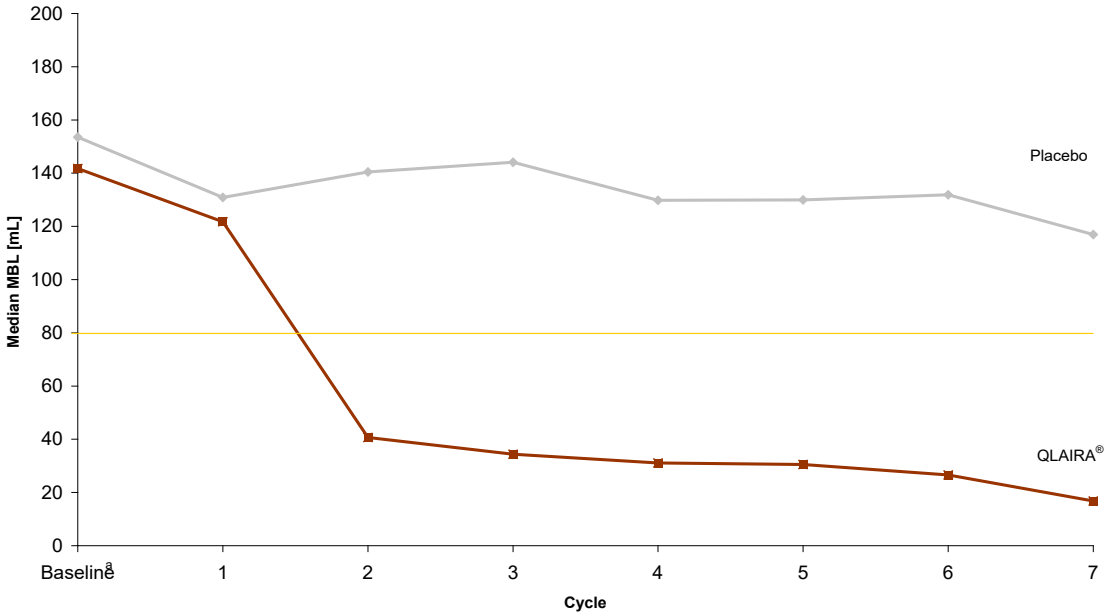
The efficacy and safety of QLAIRA for treating symptoms of dysfunctional uterine bleeding (DUB) were evaluated in two pivotal phase III multicenter, double-blind, randomised, parallel-group, placebo-controlled clinical trials (308960/A29849 and 308961/A42568). The placebo-controlled design was chosen because no oral contraceptive is approved for treatment of heavy and/or prolonged menstrual bleeding. Both studies were identical in design. Women, 18 years of age or older, with a diagnosis of dysfunctional uterine bleeding characterised by heavy (defined as two or more bleeding episodes each with menstrual blood loss of at least 80 mL during a 90-day interval), prolonged (defined as two or more bleeding episodes each lasting 8 or more days during a 90-day interval) and/or frequent bleeding (defined as more than 5 bleeding episodes with a minimum of 20 bleeding days overall during a 90-day interval) without organic pathology who desire oral contraception were included. Overall, a total of 421 women were randomised to the two clinical studies, i.e. 269 women in the QLAIRA group and 152 women in the placebo group for seven 28-day cycles.

The primary efficacy variable was the proportion of subjects who were completely relieved of symptoms, which was defined by the number of subjects with the absence of any DUB symptom and who had met all the relevant criteria for success during the 90-day efficacy assessment phase. In both studies, QLAIRA was effective in treating the symptoms of dysfunctional uterine bleeding with a point estimate of the proportion of subjects with complete symptom relief of 29% in the QLAIRA group compared to 2% in the placebo group (difference 27%; CI of the difference 21% - 33%; $p<0.0001$). In subjects with evaluable response, i.e. excluding non-responders due to missing data, the point estimate for the

proportion of subjects with complete symptom relief was 42% (CI = 35% to 49%) in the QLAIRA group compared to 3% (CI = 1% to 8%) in the placebo group (p<0.0001).

Both studies demonstrated a clinically significant decrease in menstrual blood loss (MBL). In the QLAIRA group, the median decrease in the 90-day efficacy phase compared to the 90-day run-in phase was 343 mL. The decrease in the placebo group was 62 mL. The difference between the groups was statistically significant (p<0.0001). After 6 months of treatment the median 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. The decrease in MBL achieved with QLAIRA is rapid (in Cycle 2 the median MBL was 41 mL in the QLAIRA group compared to 140 mL in the placebo group) and sustained with no loss of the effect (in Cycle 7 the median MBL in the QLAIRA group was 17 mL compared to 117 mL in the placebo group). The data show that even non-responders in the QLAIRA group had a marked decrease in MBL volume (in Cycle 2 and Cycle 7 the median MBL was 55 mL and 27 mL respectively in the QLAIRA group compared to 143 mL and 124 mL respectively in the placebo group). Figure 1 display the median MBL volume by cycle based on pooled data from studies 308960/A29849 and 308961/A42568.

Figure 1: Median MBL volume by cycle - pooled data from studies 308960/A29849 and 308961/A42568



[a] Baseline comprised MBL for 90 days. For comparative purposes, baseline was divided by 90/28.
The yellow line depicts the threshold for menorrhagia, i.e. 80 mL.

The decrease in menstrual blood loss in the QLAIRA group was accompanied by a statistically significant improvement in iron metabolism parameters (haemoglobin, haematocrit and ferritin). After 196 days of treatment the adjusted mean change from baseline in haemoglobin, haematocrit and ferritin concentrations were 0.640 g/dL, 1.47% and 7.036 ng/mL respectively in the QLAIRA group compared to 0.121 g/dL, 0.068% and 1.043 ng/mL respectively in the placebo group (p<0.0001, p=0.0002 and p<0.0001 respectively).

The decrease from baseline in the median number of bleeding days for the efficacy phase was 4 days in the QLAIRA group and 2 days in the placebo group.

The mean numbers of total sanitary protection items used during the 90-day run-in phase (baseline) were 85 in the QLAIRA group and 89 in the placebo group. The decrease in mean numbers during the efficacy phase was larger in the QLAIRA group than in the placebo group. In the QLAIRA group, the decrease was 41 (SD 35); in the placebo group, the decrease was 19 (SD 37). The difference between treatment groups in adjusted means (-22) was statistically significant ($p<0.0001$; 95% CI = -31 to -14).

The proportion of patients with improvements in DUB symptoms, on a scale of 1 (very much improved) to 7 (very much worse), at treatment day 196 as compared to study admission, was statistically significantly higher in the QLAIRA group than in the placebo group, according to both the investigator's global assessment (83% vs. 41%, $p<0.0001$) and the patient's overall assessment (79% vs. 42%, $p<0.0001$).

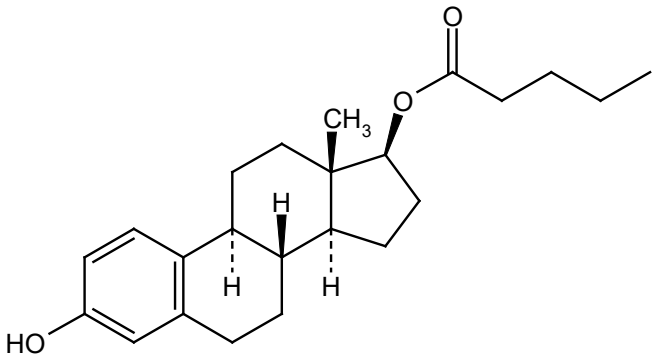
The impact of QLAIRA on quality of life (QoL) and overall well-being was assessed using the Psychological General Well-Being Index (PGWBI), the McCoy Female Sexuality Questionnaire (MFSQ) and the EuroQoL 5 Dimensional Health Questionnaire (EQ-5D). In all QoL instruments used, only small differences from baseline and between treatment groups were observed and the differences were not considered clinically relevant.

Overall, QLAIRA treatment was associated with a clinically and statistically significant disappearance of symptoms of dysfunctional uterine bleeding, essentially manifested as heavy and/or prolonged bleeding. These results were consistent and reproducible across both pivotal studies. The decreased menstrual blood loss experienced by subjects on QLAIRA was significantly better than placebo and was associated with a decrease in the number of bleeding days. The decreased menstrual blood loss was rapid, as soon as the second cycle of treatment, and sustained over 7 cycles with no signs of waning, and was positively felt by subjects. QLAIRA subjects experienced a significant decrease in the use of sanitary protection as well as a statistically significant, reproducible, and consistent improvement in parameters of iron metabolism.

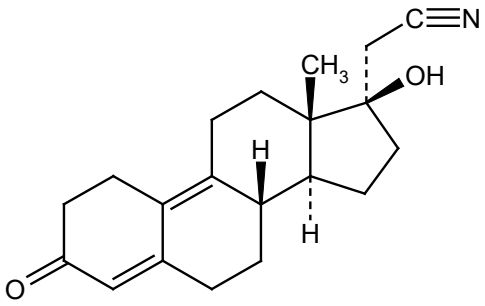
5.2 Pharmacokinetic properties

QLAIRA is a combined oral contraceptive (COC) pill containing the estrogen estradiol valerate and the progestogen dienogest.

Estradiol valerate is 1,3,5(10)-estratriene-3,17β-diol-17-valerate. The chemical formula is $C_{23}H_{32}O_3$, molecular weight 356.5 and CAS No 979-32-8. The chemical structure of estradiol valerate is as follows:



Dienogest is a progestogen. The chemical name for dienogest is 17α-cyanomethyl-17β-hydroxy-4,9-estradien-3-one. The chemical formula is $C_{20}H_{25}NO_2$, molecular weight 311.42 and CAS No 65928-58-7. The chemical structure of dienogest is as follows:



Estradiol valerate exists as white to yellowish-white crystals or crystalline powder. The substance is freely soluble in acetone and dichloromethane, soluble in ethanol, methanol, dioxane and diethylether, very slightly soluble in n-hexane and practically insoluble in petroleum ether and water. The melting point is 143 °C to 150 °C.

Dienogest exists as a white to off-white crystalline powder. The substance is freely soluble in dimethylsulfoxide, sparingly soluble in acetone and methanol, slightly soluble in ethanol and ethyl acetate and practically insoluble in water. The melting point is 210 °C to 218 °C.

- **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.

Distribution

A relatively high fraction (10%) of circulating dienogest is present in the free form, with approximately 90% being bound non-specifically to albumin. Dienogest does not bind to the specific transport proteins SHBG and CBG (corticosteroid binding globulin), therefore there is no possibility of testosterone being displaced from its SHBG-binding or cortisol from its CBG-binding. Any influence on physiological transport processes for endogenous steroids is consequently unlikely. The volume of distribution at steady state (V_d,ss) of dienogest is 46 L after the intravenous (IV) administration of 85 µg ^{3}H-dienogest.

Metabolism

Dienogest is nearly completely metabolised by the known pathways of steroid metabolism (hydroxylation, conjugation), with the formation of endocrinologically mostly inactive metabolites. The metabolites are excreted very quickly so that in plasma, unchanged dienogest is the dominating fraction. CYP3A4 was identified as the predominant isoenzyme catalysing the metabolism of dienogest. The total clearance following the IV administration of ^{3}H-dienogest was calculated as 5.1 L/h.

Elimination

The plasma half-life of dienogest is approximately 11 hours. Dienogest metabolites are excreted in the urine and faeces in a ratio of about 3:1 after oral administration of 0.1 mg/kg. Following oral administration, 42% of the dose is eliminated within the first 24h and 63% within 6 days by renal excretion. A combined 86% of the dose is excreted via urine and faeces 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 (0-24 h) 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. Further metabolism of estradiol gives rise to 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 metabolism and a considerable part of the dose administered is already metabolised in the gastrointestinal mucosa. Together with the presystemic metabolism in the liver, about 95% of the orally administered dose becomes metabolised before entering the systemic circulation. CYP3A4 is involved in the metabolism of estradiol. 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 1.2L/kg was determined after IV administration.

Elimination

The plasma half-life of circulating estradiol is about 90 minutes. 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 13-20h. Estradiol and its metabolites are mainly excreted in urine, with about 10% being excreted in the faeces.

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

5.3 Preclinical safety data

Genotoxicity

There is limited evidence available in the literature suggesting that 17β-estradiol may be weakly genotoxic at high doses. No evidence could be found for an increase in the rate of gene mutation in bacterial or mammalian cells, but there was some evidence for the induction of chromosomal aberrations and aneuploidy in mammalian cells, and two groups reported an increased incidence of sister chromatid exchanges, indicative of DNA damage. Neither of these latter effects were induced by 17β-estradiol in human lymphocyte cultures. Importantly, there was no evidence of micronuclei formation in well controlled rodent bone marrow assays.

Dienogest did not exhibit any evidence of genotoxic potential in assays for gene mutations in bacterial or mammalian cells, in *in-vitro* and *in-vivo* assays for clastogenicity and in an unscheduled DNA synthesis assay.

Carcinogenicity

The most important risk factor for cervical cancer is persistent human papillomavirus (HPV) infection. Some epidemiological studies have indicated that long-term use of COCs may further contribute to this increased risk but there continues to be controversy about the extent to which this finding is attributable to confounding effects, e.g. cervical screening and sexual behaviour including use of barrier contraceptives.

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

Malignancies may be life-threatening or may have a fatal outcome.

No long-term animal studies on the carcinogenic potential of QLAIRA have been performed. However, studies have been performed for 17β-estradiol and dienogest, the active components of QLAIRA.

Supra-physiological doses of 17β-estradiol have been associated with the induction of tumours in estrogen-dependent target organs in all rodent species tested. The relevance of these findings with respect to humans has not been established.

Long-term studies in rats and mice with dienogest showed increased incidences of pituitary adenomas, fibroepithelial mammary tumours, stromal polyps of the uterus and malignant lymphoma, at doses corresponding to exposure levels about 9-12 times that anticipated at the maximum recommended clinical dose, based on AUC. Similar tumours have been shown to develop with other estrogenic/progestogenic compounds. The tumours are thought to result from marked species differences in the optimal estrogen:progestogen ratio for

reproductive function. Dienogest showed no tumour promoter activity in the rat liver foci assay at exposure levels corresponding to about 100 times the estimated human exposure at the clinical dose, based on AUC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

QLAIRA active tablets contain the following excipients:

- lactose monohydrate
- maize starch
- pregelatinised maize starch
- povidone 25
- magnesium stearate
- hypromellose
- macrogol 6000
- talc
- titanium dioxide
- iron oxide yellow and/or iron oxide red

Placebo tablets contain:

- lactose monohydrate
- maize starch
- povidone 25
- magnesium stearate
- hypromellose
- talc
- titanium dioxide

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store at or below 30°C

6.5 Nature and contents of container

QLAIRA tablets are available as packs of 3 x 28 film-coated tablets consisting of 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 and 2 white placebo tablets.

Blister packs consisting of transparent films made of polyvinyl chloride and metallic foils made of hard tempered aluminium (mat side hot sealable). The blister is glued into a cardboard wallet.

Presentation:
Wallet containing 28 tablets

6.6 Special precautions for disposal

No special requirements.

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

7. MEDICINE SCHEDULE

Prescription only medicine

8. SPONSOR

Bayer New Zealand Limited
B:HIVE Building, 74 Taharoto Rd
Smales Farm, Takapuna
Auckland, 0622
New Zealand

Free phone: 0800 229 376

9. DATE OF FIRST APPROVAL

18 February 2010

10. DATE OF REVISION OF THE TEXT

24 July 2024

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.2	Editorial update to management of missed tablets.
6.5	Deletion of 1 x 28 pack.
8	Sponsor's contact details updated.

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