Applicant/PHRC:	***Bayer (Pty) Ltd***	*Dosage form:*	Film-coated tablet
Product proprietary name:	**QLAIRA**	*Strength:*	Phase 1: 2 dark yellow tablets, each containing: estradiol valerate 3 mg. Phase 2: 5 medium red tablets, each containing: estradiol valerate 2 mg plus dienogest 2 mg. Phase 3: 17 light yellow tablets, each containing: estradiol valerate 2 mg plus dienogest 3 mg. Phase 4: 2 dark red tablets, each, containing: estradiol valerate 1 mg. Phase 5: 2 white placebo tablets

SCHEDULING STATUS: S3

PROPRIETARY NAME AND DOSAGE FORM:

QLAIRA
Film-coated tablets

COMPOSITION:

Actives:
Estradiol valerate/dienogest
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 val423erate and 3 mg dienogest,
2 dark red tablets each containing 1 mg estradiol valerate,
2 white placebo tablets.

List of excipients:
Active tablets:
Lactose monohydrate, maize starch, pregelatinised maize starch, povidone 25, magnesium stearate, hypromellose, macrogol 6000, talc, titanium dioxide (E171, CI 77891), ferric oxide yellow (E172, CI 77492) and/or ferric oxide red (E172, CI 77491).
Placebos:
Lactose monohydrate, maize starch, povidone 25, magnesium stearate, hypromellose, talc, titanium dioxide.

PHARMACOLOGICAL CLASSIFICATION:

A 18.8 Ovulation controlling agents
ATC code: G03A

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

The contraceptive effect of combined oral contraceptives (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 the cervical secretion.
The estrogen in QLAIRA is estradiol valerate, a prodrug of the human 17ß-estradiol.
Dienogest is a progestogen (*in vitro*) which has additional antiandrogenic partial effects. Its estrogenic, antiestrogenic and androgenic properties are negligible.

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Pharmacokinetic properties:

- Dienogest

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

Distribution:
A relatively high fraction of 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. The volume of distribution at steady-state (Vd,ss) of dienogest is 46 l after the intravenous administration of 85 µg 3H-dienogest.

Metabolism:
Dienogest is nearly completely metabolised by hydroxylation and 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. The total clearance following the intravenous administration of 3H-dienogest was calculated as 5.1 l/h.

Elimination:
The plasma half-life of dienogest is approximately 11 hours. Dienogest is excreted in the form of metabolites which are excreted at a urinary to faecal 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 24 h and 63 % within 6 days by renal excretion. A combined 86 % of the dose is excreted by 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. Though, 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 hours 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 metabolised in the gastrointestinal mucosa.

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Together with the pre-systemic metabolism in the liver, about 95 % of the orally administered dose becomes metabolised before entering the systemic circulation. The main metabolites are estrone, estrone sulphate and estrone glucuronide.

Distribution:
In serum 38 % of estradiol is bound to SHBG, 60 % to albumin and 2 to 3 % circulate in free form. Estradiol can 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 minutes. Because of the large circulating pool of estrogen sulphates 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 hours to 20 hours. 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.

Preclinical safety data:

Preclinical data reveal no special risks for humans based on conventional studies of repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction. However, it is well known that sex steroids can promote the growth of certain hormone dependent tissues and tumours.

INDICATIONS:

Oral contraception.

CONTRA-INDICATIONS:

QLAIRA 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 QLAIRA use, the product should be stopped immediately.

- Presence or a history of venous or arterial thrombotic/thromboembolic events (e.g. deep venous thrombosis, pulmonary embolism, myocardial infarction) or of a cerebrovascular accident.
- Presence or history of prodromal signs of thrombosis (e.g. transient ischaemic attack, angina pectoris).
- History of migraine with focal neurological symptoms.
- Diabetes mellitus with vascular involvement.

- Presence of severe or multiple risk factor(s) for venous or arterial thrombosis.
- Pancreatitis or a history thereof if associated with severe hypertriglyceridaemia.
- Presence or history of 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) or a family history thereof.
- Undiagnosed vaginal bleeding.
- Known or suspected pregnancy.
- Hypersensitivity to the active substances or to any of the excipients.

WARNINGS:

If any of the conditions/risk factors mentioned below are present, the benefits of QLAIRA use should be weighed against the possible risks for each individual woman and discussed with her 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 use should be discontinued.

No epidemiological studies on the effects of estradiol/estradiol valerate containing COCs exist. All the following warnings and precautions are derived from clinical and epidemiological data of ethinylestradiol. Whether these warnings and precautions apply to QLAIRA is unknown.

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.

Venous thromboembolism (VTE), manifesting as deep venous thrombosis and/or pulmonary embolism, may occur during the use of QLAIRA. The risk for venous thromboembolism is highest during the first year a woman ever uses QLAIRA. The approximate incidence of VTE in users of low oestrogen dose (< 0.05 mg ethinylestradiol) OCs is up to 4 per 10 000 woman years compared to 0.5 to 3 per 10 000 woman years in non-OC users. The incidence of VTE associated with pregnancy is 6 per 10 000 pregnant woman years.

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 QLAIRA.

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 of venous or arterial thrombotic/thromboembolic events or of a cerebrovascular accident

increases with:

- age;
- smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age);
- a positive family history (i.e., venous or 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 QLAIRA use;
- obesity (body mass index over 30 kg/m^2);
- dyslipoproteinaemia;
- hypertension;
- migraine;
- valvular heart disease;
- atrial fibrillation;
- prolonged immobilisation, major surgery, any surgery to the legs, or major trauma. In these situations, it is advisable to discontinue QLAIRA use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilisation.

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

An increased risk of thromboembolism in the puerperium must be considered (see "Pregnancy and lactation").

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

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

Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include Activated Protein C (APC) resistance, hyperhomocysteinaemia, antithrombin-III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).

When considering risk/benefit, the doctor should take into account that adequate treatment of a condition may reduce the associated risk of thrombosis and that the risk associated with pregnancy is higher than that associated with low-dose COCs (< 0.05 mg ethinylestradiol).

Tumours:

The most important risk factor for cervical cancer is persistent HPV infection. Some epidemiological studies have indicated that long-term use of COCs may further contribute to this increased risk.

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 haemorrhages. A hepatic 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 QLAIRA.

Other conditions:

Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when using QLAIRA.

Increases in blood pressure have been reported in many women taking COCs. If a sustained clinically significant hypertension develops during the use of QLAIRA then it is prudent for the doctor to withdraw QLAIRA and treat the hypertension. Where considered appropriate, QLAIRA 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: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; gestational herpes; 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 QLAIRA 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 QLAIRA.

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 QLAIRA.

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

Medical examination/consultation:

A complete medical history and physical examination should be taken prior to the initiation or reinstitution of QLAIRA use, guided by the "Contra-indications" and "Warnings" and it should be repeated periodically. Periodic medical assessment is also of importance because contra-indications

(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 QLAIRA. 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 diseases.

Reduced efficacy:

The efficacy of QLAIRA may be reduced for example in the following events: missed active tablets (section "Management of missed tablets"), gastrointestinal disturbances (section "Advice in case of gastrointestinal disturbances") during active tablet taking or concomitant medication (section "Interactions").

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. 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 QLAIRA has been taken according to the directions described in section "Dosage and directions for use", it is unlikely that the woman is pregnant. However, if QLAIRA 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 QLAIRA use is continued.

INTERACTIONS:

Interaction studies have only been performed in adults.

Interactions of other medicinal products with QLAIRA:

Interactions between oral contraceptives and other medicines 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.

Hepatic metabolism: Interactions can occur with medicines (e.g., phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St. John's wort) that induce microsomal enzymes (e.g., cytochrome P450 enzymes) which can result in increased clearance of sex hormones. HIV protease (e.g., ritonavir) and non-nucleoside reverse transcriptase inhibitors (e.g., nevirapine), and combinations of them, have also been reported to potentially affect hepatic metabolism.

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Dienogest in QLAIRA, is a substrate of cytochrome P450 (CYP) 3A4. The effect of the CYP3A4 inducer rifampicin was studied in healthy postmenopausal women. Co-administration of rifampicin with QLAIRA 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 (0-24 hours), were decreased by 83 % and 44 %, respectively.

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

In a study investigating the effect of CYP3A4 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 (0-24 hours) at steady state for dienogest and a 57 % increase for estradiol. When co-administered with the moderate inhibitor erythromycin, the AUC (0-24 hours) of dienogest and estradiol at steady state were increased by 62 % and 33 %, respectively.

Interference with enterohepatic circulation: Enterohepatic circulation of estrogens may decrease when certain antibiotic agents are given which may reduce estradiol concentrations (e.g., penicillins, tetracyclines).

Women on treatment with microsomal enzyme-inducing medicines or with antibiotics should temporarily use a barrier method in addition to QLAIRA or choose another method of contraception. The barrier method should be used during the time of concomitant medicine administration and for 28 days after its discontinuation.

Interactions of QLAIRA with other medicinal products:

Oral contraceptives may affect the metabolism of certain other medicines (e.g., lamotrigine) and may result in either increased or decreased plasma and tissue concentrations. However, based on the *in vitro* data, 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.

PREGNANCY AND LACTATION:

QLAIRA is contra-indicated in pregnancy. If pregnancy occurs during use of QLAIRA, further intake should be stopped.

Lactation may be influenced by QLAIRA as it may reduce the quantity and change the composition of breast milk. The use of QLAIRA should 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.

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Use in children:

QLAIRA is not intended for girls under the age of 18 years.

Effects on ability to drive and use machines:

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

DOSAGE AND DIRECTIONS FOR USE:

How to take QLAIRA:

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

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).
- *When changing over from another 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. If 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 (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 needs not take additional contraceptive measures.
- *Following delivery or second-trimester abortion*
  For breastfeeding women see section "Pregnancy and lactation".
  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 QLAIRA 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:

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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 intervals.

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

Day	**Colour** **Content of estradiol valerate (EV)/ dienogest (DNG)**	**Principles to follow if missing *one* tablet for more than 12 hours:**
1 to 2 3 to 7 8 to 17	Dark yellow tablets (3.0 mg EV) Medium red tablets (2.0 mg EV + 2.0 mg DNG) Light yellow tablets (2.0 mg EV + 3.0 mg DNG)	• Take missed tablet immediately and the following tablet as usual (even if this means taking two tablets on the same day) • Continue with tablet-taking in the normal way • Use barrier contraception for the next 9 days
18 to 24	Light yellow tablets (2.0 mg EV + 3.0 mg DNG)	• Discard current wallet, and start immediately with the first pill of a new wallet • Continue with tablet-taking in the normal way • Barrier contraception for the next 9 days
25 to 26	Dark red tablets (1.0 mg EV)	• Take missed tablet immediately and the following tablet as usual (even if this means taking two tablets on the same day) • No barrier contraception necessary
27 to 28	White tablets (Placebos)	• Discard missed tablet and continue tablet-taking in the normal way • No barrier contraception necessary

If a woman has forgotten to start a new wallet, or if she has missed tablets during days 3 to 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 to 24) that are missed and the closer they are to the placebo tablet phase, the higher the risk of a pregnancy.

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

Advice in case of 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 to 4 hours after active tablet-taking, the advice concerning missed tablets is

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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.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

The table below reports adverse reactions (ARs) by MedDRA system organ classes (MedDRA SOCs). The frequencies are based on clinical trial data. The adverse reactions were recorded in 2 phase III clinical studies (N=1776 women at risk for pregnancy) and considered at least possibly causally related to QLAIRA use.

System organ class	**Common (≥ 1/100 to 1/10)**	**Uncommon (≥ 1/1000 to < 1/100)**	**Rare (≥ 1/10 000 to < 1/1 000)**
Infections and infestations		Vaginal candidiasis (0.2 %)	Herpes simplex Presumed ocular histoplasmosis syndrome Tinea versicolor
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)		Uterine leiomyoma (0.3 %)	Benign breast neoplasm Focal nodular hyperplasia
Metabolism and nutrition disorders			Increased appetite
Psychiatric disorders		Depression/depressed mood (0.8 %) Mood changes (0.3 %) Decreased libido (0.6 %) Mental disorder (0.2 %) Sleep disorder (0.1 %)	Aggression Increased libido Nervousness Restlessness
Nervous system disorders	Headache (1.9 %)	Migraine (0.5 %)	Disturbance in attention Migraine with aura Tension headache
Eye disorders			Contact lens intolerance
Vascular disorders		Hypertension (0.3 %)	Hot flush Hypotension Vein pain
Gastrointestinal disorders		Abdominal pain (0.5 %) Nausea (0.5 %)	Abdominal distension Diarrhoea Vomiting
Hepato-biliary disorders		Increased alanine aminotransferase (0.1 %)	
Skin and subcutaneous tissue disorders	Acne (2.3 %)	Alopecia (0.8 %)	Chloasma Allergic dermatitis Hirsutism Neurodermatitis

			Pigmentation disorder (pigmented spots on face) Generalised pruritus Pruritic rash Seborrhoea Skin disorder including skin tightness Urticaria
Musculoskeletal, connective tissue and bone disorders			Muscle spasms Sensation of heaviness
Reproductive system and breast disorders	Breast pain (3.5 %) Breast discomfort (1.2 %) Metrorrhagia (1.5 %)	Breast enlargement (0.3 %) Fibrocystic breast disease (0.3 %) Vaginal discharge (0.1 %) Amenorrhoea (0.1 %) Dysmenorrhoea (0.8 %) Menstrual disorder (0.2 %) Menorrhagia (0.2 %) Premenstrual syndrome (0.2 %) Cervical dysplasia (0.3 %) Ovarian cyst (0.3 %)	Breast cyst Genital haemorrhage Hypomenorrhoea Irregular menstruation Pelvic pain Vulvovaginal dryness
General disorders and administrative site conditions		Irritability (0.2 %) Malaise (0.1 %) Oedema (0.2 %)	
Investigations	Weight increased (1.3 %)	Weight decreased (0.2 %)	

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.

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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.

Applicant/PHRC:	***Bayer (Pty) Ltd***	*Dosage form:*	Film-coated tablet
Product proprietary name:	**QLAIRA**	*Strength:*	Phase 1: 2 dark yellow tablets, each containing: estradiol valerate 3 mg. Phase 2: 5 medium red tablets, each containing: estradiol valerate 2 mg plus dienogest 2 mg. Phase 3: 17 light yellow tablets, each containing: estradiol valerate 2 mg plus dienogest 3 mg. Phase 4: 2 dark red tablets, each, containing: estradiol valerate 1 mg. Phase 5: 2 white placebo tablets

IDENTIFICATION:

2 round biconvex dark yellow film-coated tablets embossed with the letters DD in a regular hexagon on one side.
5 round biconvex medium red film-coated tablets embossed with the letters DJ in a regular hexagon on one side.
17 round biconvex light-yellow film-coated-tablets embossed with the letters DH in a regular hexagon on one side.
2 round biconvex dark red film-coated-tablets embossed with the letters DN in a regular hexagon on one side.
2 round biconvex white film-coated-tablets embossed with the letters DT in a regular hexagon on one side.

PRESENTATION:

Blister packs consisting of clear transparent films made of polyvinyl chloride and metallic foils made of hard tempered aluminum. The blister is glued into a carton wallet.

Pack sizes:
1 x 28 film-coated tablets; 3 x 28 film-coated tablets; 6 x 28 film-coated tablets.

STORAGE INSTRUCTIONS:

Store at or below 30 ºC. KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

43/18.8/0591

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Bayer (Pty) Ltd
Registration No.: 1968/011192/07
27 Wrench Road
Isando
1609

DATE OF PUBLICATION OF THE PACKAGE INSERT:

30 September 2011