

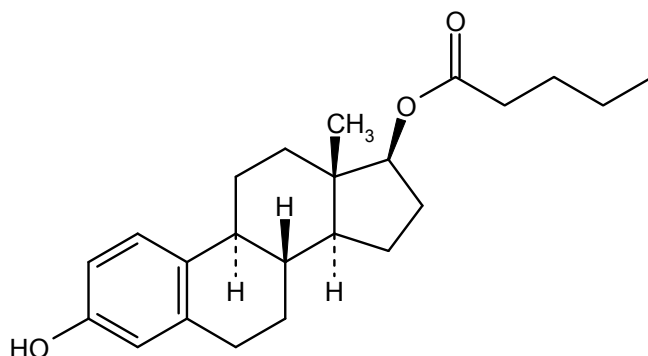
DATA SHEET

QLAIRA® (oestradiol valerate / dienogest)

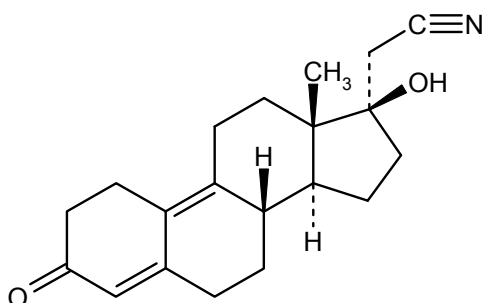
NAME OF THE MEDICINE

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

Oestradiol valerate is 1,3,5(10)-estratriene-3,17 β -diol-17-valerate. The chemical formula is C₂₃H₃₂O₃, molecular weight 356.5 and CAS No 979-32-8. The chemical structure of oestradiol valerate is as follows:



Dienogest is a progestogen. The chemical name for dienogest is 17 α -cyanomethyl-17 β -hydroxy-4,9-estradien-3-one. The chemical formula is C₂₀H₂₅NO₂, molecular weight 311.42 and CAS No 65928-58-7. The chemical structure of dienogest is as follows:



DESCRIPTION

Oestradiol 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.

QLAIRA tablets are available as packs of 1 x 28 or 3 x 28 film-coated tablets consisting of 2 dark yellow tablets each containing 3mg oestradiol valerate, 5 medium red tablets each containing 2mg oestradiol valerate and 2mg dienogest, 17 light yellow tablets each containing 2mg oestradiol valerate and 3mg dienogest, 2 dark red tablets each containing 1mg oestradiol valerate and 2 white placebo tablets. Besides the active ingredient, QLAIRA also contains 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 and titanium dioxide.

PHARMACOLOGY

Pharmacodynamics

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 **PRECAUTIONS, ADVERSE 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 (0.05mg ethinylloestradiol) have been shown to reduce the incidence of ovarian cysts, pelvic inflammatory disease, benign breast disease and ectopic pregnancy. Whether this also applies to oestradiol valerate containing COCs remains to be confirmed.

The oestrogen in QLaira is oestradiol valerate, a prodrug of the natural human 17 β -oestradiol. The oestrogenic component used in this COC is therefore different from the oestrogens usually used in COCs which are the synthetic oestrogens ethinylloestradiol 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 ethinylloestradiol/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, oestradiol 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 oestrogenic, antioestrogenic 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.

Pharmacokinetics

Dienogest

Absorption

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

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 46L after the intravenous administration of 85 μ g 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 intravenous administration of ³H-dienogest was calculated as 5.1L/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 0.1mg/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 3mg dienogest in combination with 2mg oestradiol valerate. Trough, maximum and average dienogest serum concentrations at steady state are 11.8ng/mL, 82.9ng/mL and 33.7ng/mL, respectively. The mean accumulation ratio for AUC (0-24h) was determined to be 1.24.

Oestradiol valerate

Absorption

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

Metabolism

The valeric acid undergoes very fast metabolism. After oral administration approximately 3% of the dose is directly bioavailable as oestradiol. Oestradiol 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 oestradiol. The main metabolites are oestrone, oestrone sulfate and oestrone glucuronide.

Distribution

In serum 38% of oestradiol is bound to SHBG, 60% to albumin and 2-3% circulate in free form. Oestradiol 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 i.v. administration.

Elimination

The plasma half-life of circulating oestradiol is about 90 minutes. After oral administration, however, the situation differs. Because of the large circulating pool of oestrogen sulfates and glucuronides, as well as enterohepatic recirculation, the terminal half life of oestradiol after oral administration represents a composite parameter which is dependent on all of these processes and is in the range of about 13-20h. Oestradiol and its metabolites are mainly excreted in urine, with about 10% being excreted in the faeces.

Steady-state conditions

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

CLINICAL TRIALS

Oral contraception

The contraceptive efficacy and safety of QLAIIRA 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 oestradiol valerate/dienogest (QLAIIRA) 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 QLAIIRA in comparison to a reference COC containing 0.02mg EE and 0.10mg 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 QLAIIRA 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 QLAIIRA: 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 QLAIIRA 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

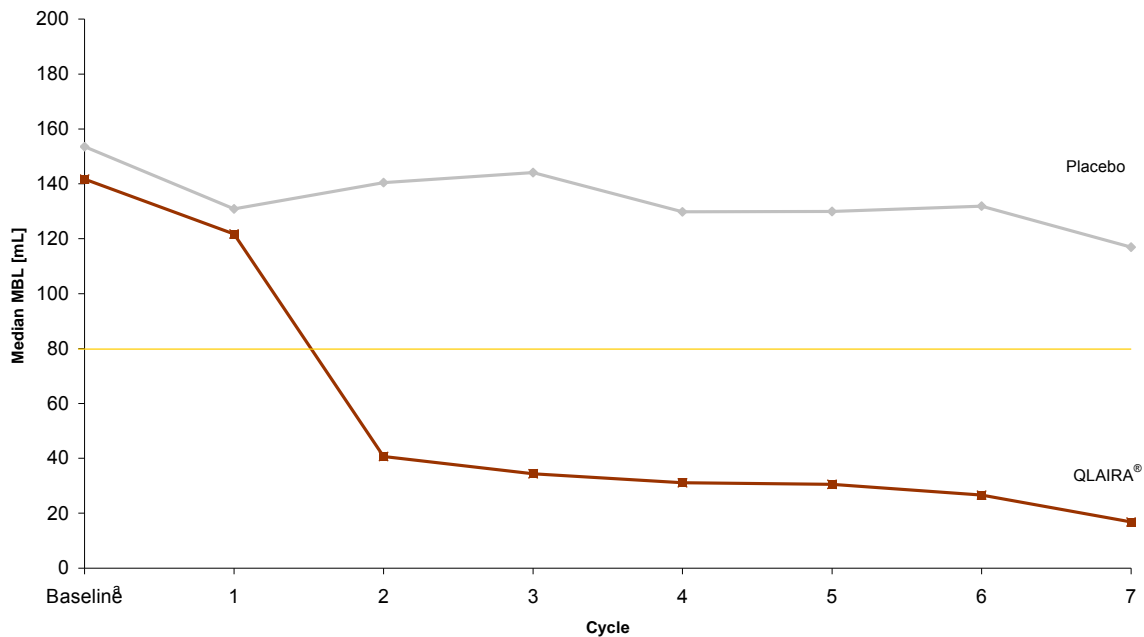
The efficacy and safety of QLAIIRA for treating symptoms of dysfunctional uterine bleeding (DUB) were evaluated in two pivotal phase III multicenter, double-blind, randomised, parallel-group, placebo-controlled clinical trials (308960/A29849 and 308961/A42568). The placebo-controlled design was chosen 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 80mL 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 QLAIIRA 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, QLAIIRA 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 QLAIIRA 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 QLAIIRA 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 QLAIIRA group, the median decrease in the 90-day efficacy phase compared to the 90-day run-in phase was 343mL. The decrease in the placebo group was 62mL. The difference between the groups was statistically significant ($p < 0.0001$). After 6 months of treatment the median MBL was decreased by 88% (from 142mL to 17mL) in the QLAIIRA group compared to 24% (from

154mL to 117mL) in the placebo group. The decrease in MBL achieved with QLAIIRA is rapid (in Cycle 2 the median MBL was 41mL in the QLAIIRA group compared to 140mL in the placebo group) and sustained with no loss of the effect (in Cycle 7 the median MBL in the QLAIIRA group was 17mL compared to 117mL in the placebo group). The data show that even non-responders in the QLAIIRA group had a marked decrease in MBL volume (in Cycle 2 and Cycle 7 the median MBL was 55mL and 27mL respectively in the QLAIIRA group compared to 143mL and 124mL 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. 80mL.

The decrease in menstrual blood loss in the QLAIIRA 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 0.640g/dL, 1.47% and 7.036ng/mL respectively in the QLAIIRA group compared to 0.121g/dL, 0.068% and 1.043ng/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 QLAIIRA 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 QLAIIRA group and 89 in the placebo group. The decrease in mean numbers during the efficacy phase was larger in the QLAIIRA group than in the placebo group. In the QLAIIRA 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 QLAIIRA 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.

INDICATIONS

Oral contraception.

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

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 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 prodromi of a thrombosis (e.g. transient ischaemic attack, angina pectoris)
- Presence of a severe or multiple risk factor(s) for venous or arterial thrombosis may also constitute a contraindication (see **PRECAUTIONS – Circulatory Disorders**)
- History of migraine with focal neurological symptoms
- Diabetes mellitus with vascular involvement
- 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 the active substances or to any of the excipients

PRECAUTIONS

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

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

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

Circulatory Disorders

The risk of venous thromboembolism (VTE) during use of QLAIRA is currently unknown.

Epidemiological studies have suggested an association between the use of ethinyl oestradiol containing COCs and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, deep venous thrombosis, pulmonary embolism and of cerebrovascular accidents. These events occur rarely.

The risk of VTE is highest during the first year of use. This increased risk is present after initially starting a COC or restarting (following a 4 week or greater pill free interval) the same or a different COC. 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 oestrogen dose (<50µg 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 may be life-threatening or may have a fatal outcome (in 1-2% of the cases).

Venous thromboembolism, manifesting as deep venous thrombosis and/or pulmonary embolism, may occur during the use of all COCs. A large, prospective 3-armed cohort study¹ has shown that the frequency of VTE diagnosis ranges between 8 to 10 per 10,000 woman years in low oestrogen dose (<50µg 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 users¹, and ranges between 20 to 30 per 10,000 pregnant women or post partum.^{1,3}

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

Symptoms of venous [including pulmonary embolism (PE) and deep venous thrombosis (DVT)] or arterial thrombotic / thromboembolic [including myocardial infarction (MI), vascular occlusion and cerebrovascular accident] events can include: unilateral swelling of the leg 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; slight blue discoloration of an extremity; sharp chest pain which may increase with deep breathing; 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; sudden numbness or weakness of the face, arm or leg, especially on one side of the body; sense of anxiety; sudden confusion, trouble speaking or understanding; severe light headedness or dizziness; rapid or irregular heartbeats; sudden onset of unexplained shortness of breath or rapid breathing; sudden coughing which may bring up blood; sudden, severe or prolonged headache with no known cause; sudden trouble seeing in one or both eyes; sudden trouble walking, loss of balance or coordination; loss of consciousness or fainting with or without seizure; acute abdomen; fullness, indigestion or choking feeling; sweating, nausea, vomiting.

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.

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).

Arterial thromboembolic events may be life-threatening or may have a fatal outcome.

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 known or suspected, the woman should be referred to a specialist for advice before deciding about any COC use
- obesity (body mass index over 30kg/m²)
- 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 COC 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.

The increased risk of thromboembolism in the puerperium must be considered (for information on pregnancy and lactation see **Use in pregnancy** and **Use in lactation**).

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

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

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 (<0.05mg ethinylloestradiol).

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 oestrogens 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 <0.05mg ethinyloestradiol). 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 46mg, 45mg, 48mg or 44mg of lactose per tablet, respectively. Each placebo white film-coated tablet contains 50mg 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 reinstatement 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 diseases.

Reduced efficacy

The efficacy of COCs may be reduced for example in the following events: missed active tablets (see **Management of missed tablets**), gastrointestinal disturbances during active tablet taking (see **Advise in case of gastrointestinal disturbances**) or concomitant medication (see **Interactions with other medicines**).

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.

Use in pregnancy (Category B3)

QLAIRA is contraindicated in pregnancy. If pregnancy occurs during use of QLAIRA, further intake must be stopped. However, extensive epidemiological studies with ethinyloestradiol 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 17 β -oestradiol 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.

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.

Paediatric use

QLAIRA is only indicated after menarche.

Use in the elderly

Not applicable. QLAIRA is not indicated after menopause.

Patients with hepatic impairment

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

Genotoxicity

There is limited evidence available in the literature suggesting that 17β -oestradiol 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 -oestradiol 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 QLAIIRA have been performed. However, studies have been performed for 17β -oestradiol and dienogest, the active components of QLAIIRA.

Supra-physiological doses of 17β -oestradiol have been associated with the induction of tumours in oestrogen-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 oestrogenic/progestogenic compounds. The tumours are thought to result

from marked species differences in the optimal oestrogen:progesterone 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.

Interactions with other medicines

Effects of other medicinal products on QLIRA

Interactions of other medicines (enzyme inducers, some antibiotics) with oral contraceptives may lead to breakthrough bleeding and/or contraceptive failure. Women receiving treatment with microsomal enzyme-inducing medicines or with antibiotics 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 diminishing the efficacy of COCs (enzyme-inducers and antibiotics)

- *Enzyme induction (increase of hepatic metabolism)*: Interactions can occur with medicines that induce microsomal enzymes (e.g. cytochrome P450 enzymes) which can result in increased clearance of sex hormones (e.g. phenytoin, 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 oestradiol valerate/dienogest tablets led to significant decreases in steady state concentrations and systemic exposures of dienogest and oestradiol. The systemic exposure of dienogest and oestradiol at steady state, measured by AUC (0-24h), were decreased by 83% and 44%, respectively.

Also, HIV protease (e.g. ritonavir) and non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine), and combinations of them, have been reported to potentially increase hepatic metabolism.

- *Antibiotics (interference with enterohepatic circulation)*: Some clinical reports suggest that enterohepatic circulation of oestrogens may decrease when certain antibiotic agents are given, which may reduce oestradiol concentrations (e.g. penicillins, tetracyclines).

Substances interfering with the metabolism of combined hormonal contraceptives (enzyme inhibitors)

Dienogest is a substrate of cytochrome P450 (CYP) 3A4. Known CYP 3A4 inhibitors like azole antifungals (e.g. ketoconazole), cimetidine, verapamil, macrolides (e.g. erythromycin), diltiazem, antidepressants and grapefruit juice may increase plasma levels of dienogest.

In a study investigating the effect of CYP 3A4 inhibitors (ketoconazole, erythromycin), steady state dienogest and oestradiol 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 oestradiol. When co-administered with the moderate inhibitor erythromycin, the AUC (0-24h) of dienogest and oestradiol at steady state were increased by 62% and 33%, respectively.

Effects of QLIRA 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 QLIRA is unlikely at the therapeutic dose.

Note: The product information of concomitant medications should be consulted to identify potential interactions.

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.

ADVERSE EFFECTS

Summary of safety profile

The most commonly reported adverse drug reactions (ADRs) with QLAIRA when used as an oral contraceptive or in the treatment of heavy and/or prolonged menstrual bleeding in women without organic pathology who desire oral contraception are nausea, breast pain and unscheduled uterine bleeding. They occur in >2% of users.

Serious adverse drug reactions are arterial and venous thromboembolism.

The most serious undesirable effects associated with the use of COCs are described under **PRECAUTIONS**.

The frequencies of ADRs reported in Phase II and III clinical studies with QLAIRA as an oral contraceptive (N = 2423) and in the treatment of heavy and/or prolonged menstrual bleeding in women without organic pathology who desire oral contraception (N = 264) are summarised in the table below by MedDRA system organ classes. Within each frequency grouping, undesirable effects are presented in order of decreasing frequency. Frequencies are defined as common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$) and rare ($1/10,000$ to $< 1/1,000$). All ADRs listed in the rare category occurred in 1 to 2 volunteers resulting in $< 0.1\%$.

Table 1: Adverse drug reactions, Phase II and III clinical studies, N = 2687 women (100%)

System Organ Class	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1,000$ to $< 1/100$)	Rare ($\geq 1/10,000$ to $< 1/1,000$)
Psychiatric disorders	Depression / depressed mood (1.6%) Emotional lability (1.4%) Decrease and loss of libido (1.1%)		
Nervous system disorders	Migraine (1.9%)		
Vascular disorders			Venous and arterial thromboembolic events* ($< 0.1\%$)
Gastrointestinal disorders	Nausea (3.1%)		
Reproductive system and breast disorders	Breast pain (5.8%) Unscheduled uterine bleeding (4.4%)	Genital tract bleeding (0.4%)	

* Myocardial infarction ($< 0.1\%$), deep vein thrombosis ($< 0.1\%$)

Venous and arterial thromboembolic events summarizes the following Medical Entities: peripheral deep venous occlusion, thrombosis and embolism / pulmonary vascular occlusion, thrombosis, embolism and infarction / myocardial infarction / cerebral infarction and stroke not specified as haemorrhagic or ischemic

The comparative rates for adverse reactions for treatment (N=399) in comparison to the reference COC containing 0.02mg EE and 0.10mg 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%).

In addition to the above mentioned adverse reactions, erythema nodosum, erythema multiforme, breast discharge and hypersensitivity have occurred under treatment with ethinyl oestradiol 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 oestrogens may induce or exacerbate symptoms of angioedema.

DOSAGE AND 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 **PRECAUTIONS**.

Women should be advised to start at day 21 to 28 after delivery or second-trimester abortion. When starting later, the woman should be advised to additionally use a barrier method for the first 9 days of tablet-taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of COC use or the woman has to wait for her first menstrual period.

Management of missed tablets

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

The following advice only refers to missed active tablets:

If the woman is **less than 12 hours** late in taking any tablet, contraceptive protection is not reduced. The woman should take the tablet as soon as she remembers and should take further tablets at the usual time.

If she is **more than 12 hours** late in taking any tablet, contraceptive protection may be reduced. The woman should take the last missed tablet as soon as she remembers, **even if this means taking two tablets at the same time**. She then continues to take tablets at her usual time.

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

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

OVERDOSAGE

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.

PRESENTATION AND STORAGE CONDITIONS

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

Pack sizes:

1 x 28 film-coated tablets

3 x 28 film-coated tablets

NAME AND ADDRESS OF THE SPONSOR

Bayer New Zealand Limited
3 Argus Place, Hillcrest
North Shore, Auckland 0627
New Zealand

Free phone: 0800 233 988

MEDICINE CLASSIFICATION

PRESCRIPTION ONLY MEDICINE

DATE OF PREPARATION

1 December 2010

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