Australian Government

Department of Health and Ageing

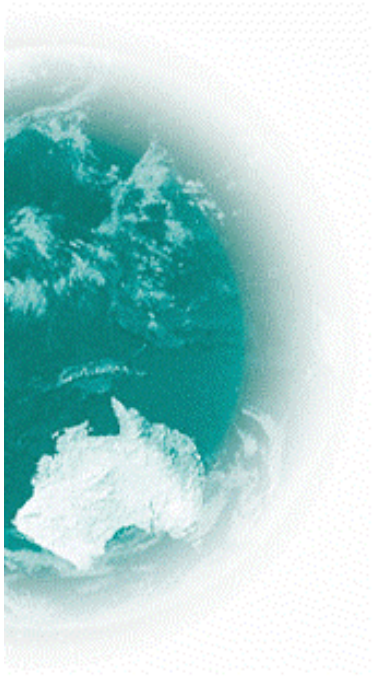
Therapeutic Goods Administration

Australian Public Assessment Report for Oestradiol valerate/Dienogest

Proprietary Product Name: Qlaira

Submission No: PM-2009-02910-3-5

Sponsor: Bayer Australia Limited



March 2011

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	Extension of Indications
Decision:	Approved
Date of Decision:	9 November 2010
Active ingredient(s):	Oestradiol valerate Dienogest
Product Name(s):	Qlaira
Sponsor's Name and Address:	Bayer Australia Limited 875 Pacific Highway Pymble NSW 2073
Dose form(s):	Film-coated tablets
Strength(s):	Each pack contains oestradiol valerate 3 mg (2 tablets), oestradiol valerate 2 mg/dienogest 2 mg (5 tablets), oestradiol valerate 2 mg/dienogest 3 mg (17 tablets), oestradiol valerate 1 mg (2 tablets), placebo (2 tablets).
Container(s):	Blister pack glued into a cardboard wallet
Pack size(s):	1 x 28 tablets, 3 x 28 tablets
Approved Therapeutic use:	Contraception Treatment of heavy and/or prolonged menstrual bleeding in women without organic pathology who desire oral contraception.
Route(s) of administration:	Oral
Dosage:	One tablet daily in the order directed on the wallet pack.
ARTG Number (s)	149319

Product Background

Qlaira is the combination of oestradiol valerate and dienogest (EV/DNG) and was originally considered by the Australian Drug Evaluation Committee (ADEC) at its 263rd meeting and following a positive recommendation, it was registered in Australia for oral contraception. The current application sought to extend the indications to include:

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

At present, there are no medicines that are registered in Australia for the treatment of dysfunctional uterine bleeding (DUB). Non-steroidal anti-inflammatory drugs, tranexamic acid, danazol, progestins, combined oral contraceptives and GnRH agonists are used to treat this condition, with varying degrees of efficacy.

Regulatory Status

The product received initial ARTG Registration in 2009.

A similar application to the current Australian submission has been submitted in USA, Canada, Switzerland and all European Union (EU)/European Economic Area countries except Liechtenstein

(Variation Type II procedure). The decentralized procedure for the indication 'treatment of heavy menstrual bleeding in women without organic pathology who desire oral contraception' in the European Union (EU)/European Economic Area was favourably concluded in October 2010 and first national approvals have subsequently been granted. Applications in all other countries are pending.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Quality Summary and Conclusions

There was no requirement for a quality evaluation in an application of this type.

III. Nonclinical Findings

Nonclinical Summary and Conclusions

There was no requirement for a nonclinical evaluation in an application of this type.

IV. Clinical Findings

Introduction

The submission consisted of two studies of "nearly identical design" to support the product's use in dysfunctional uterine bleeding (DUB). These are studies A29849 and A42568. In addition, one study was submitted to update the Clinical trials section on the already approved indication, oral contraception. The advice of the Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC) was requested regarding the extension of indication (dysfunctional uterine bleeding) only and only this aspect will be discussed in this AusPAR.

Pharmacokinetics/Pharmacodynamics

No new pharmacokinetic/pharmacodynamic data were included in the submission.

Efficacy

Introduction

There were two clinical trials submitted in support of DUB: Study 308960/A29849 summarised in Table 1; and Study 308961/A42568 summarised in Table 7. In addition, a pooled analysis of the efficacy data from these two studies was provided in the form of tabulations in a Biometrical Report of Efficacy for DUB.

Study 308960/A29849

Study 308960/A29849 was a multicentre, double blind, randomised, parallel group, placebo controlled, Phase III Clinical Trial of efficacy and safety of EV/DNG in subjects with DUB (Table 1). The study aimed to investigate the treatment of prolonged, excessive, or frequent uterine bleeding in women without organic pathology who desire oral contraception. The study was coordinated by Bayer Schering Pharma Ag and conducted at 47 centres: 37 in the US and 10 in Canada.

The inclusion criteria are summarised in Table 1. There was an extensive list of exclusion criteria which is shown in Table 2.

Table 1: Study 308960/A29849

Number of subjects with age and sex	**Diagnosis + criteria for inclusion/exclusion**	**Duration of Treatment**	**Test Product Dosage Regimen Route of administration, Formulation**	**Criteria for evaluation**	**Results (efficacy)**	**Adverse Reactions**
1077 subjects were screened, 887 subjects failed screening and 190 subjects were randomised: 120 to EV/DNG and 70 to placebo All subjects were female with an age range of 20 to 53 years	≥18 years of age with DUB defined as at least one of the following symptoms within the 90-day run-in phase • Prolonged bleeding: 2 or more bleeding episodes • Frequent bleeding: greater than 5 bleeding episodes, with a minimum of 20 bleeding days overall • Excessive bleeding: 2 or more bleeding episodes each with blood loss volume of 80 mL or more Willing to use barrier contraception (eg, condoms) from screening through study completion Normal or clinically insignificant Pap smear results. Endometrial biopsy during the run-in phase or a valid endometrial biopsy performed within 6 months of visit 1, without evidence of malignancy or atypical hyperplasia	7 cycles of 28 Days (196 Days) Preceded by a 90 Day run-in phase and followed by a 30 Day follow-up phase	Sequential regimen comprising 28 tablets per cycle taken in the following order: - 1 tablet daily containing 3.0 mg EV for 2 days - 1 tablet daily containing 2.0 mg EV+ 2.0 mg DNG for 5 days - 1 tablet daily containing 2.0 mg EV + 3.0 mg DNG for 17 days - 1 tablet daily containing 1.0 mg EV for 2 days - 1 tablet daily containing placebo for 2 days	The primary efficacy variable was the overall success rate, The secondary efficacy variables were the: Proportion of patients cured from each individual symptom Change in blood loss volume for all patients and for patients with excessive bleeding Change in number of bleeding days and bleeding episodes Change in number of sanitary protection used Proportion of patients with improvement in the Investigator's global assessment scale Proportion of patients with improvement in the patient's overall assessment scale	For the primary efficacy outcome variable the difference in the proportion of responders between treatment groups was 0.2631, p <0.0001, OR (95% CI) 13.417 (3.1240 to 57.626). There was a higher proportion of subjects in the Qlaira group with excessive bleeding that responded: 29 (44.62%) compared with two (4.76%). The change from baseline in adjusted mean blood loss was higher in the Qlaira group. There was a greater decrease in number of sanitary protection items: mean (SD) -43.6 (40.90) for Qlaira and -21.1 (43.24) for placebo; mean difference (95% CI) -23.4 (-38.69 to -8.03). p <0.0001. A greater proportion of subjects in the Qlaira group had an improvement in Investigator's and Patient's Global Scale at Day 196: p <0.0001. From baseline to Day 196, there were increases in haematocrit, ferritin and haemoglobin in the Qlaira group compared with placebo	TEAEs were reported in 80 (67.2%) subjects in the EV/DNG group and 36 (54.5%) in the placebo group. The most commonly reported TEAEs in the EV/DNG group were: nasopharyngitis, acne, metrorrhagia, nausea, and bacterial vaginitis. 2 (1.1%) experienced SAEs; one each in the EV/DNG (myocardial infarction) and placebo (suicide attempt) groups. No deaths were reported. 11 (9.2%) subjects in the EV/DNG group and 4 (6.1%) in the placebo group discontinued because of AEs.

The active study treatment is described in Table 1. The sequential regimen is the same as that proposed in the draft PI. In both groups, the study treatment phase was preceded by a 90 day run-in phase and was followed by a 30 day follow-up phase. There were seven treatment cycles of 28 days (196 days in total). Subjects were block randomised by centre, in a 2:1 ratio (treatment: placebo) by sequential randomisation number.

Table 2: Exclusion criteria for Study 308960/A29849

Current diagnosis of organic uterine bleeding such as von Willebrand disease, chronic endometritis, adenomyosis, endometriosis, endometrial polyps, endometrial carcinomas, mixed mullerian mesenchymal tumors, leiomyomas, leiosarcomas, or endometrial stromal tumors
Signs of hirsutism
Atypical hyperplasia
History of endometrial ablation, or dilatation and curettage within 2 months of Visit 1
Clinically significant abnormal TVU results
Clinically significant abnormal results of breast examination
Positive pregnancy test
Pregnancy, lactation, or abortion within 3 months of Visit 1
Not willing to discontinue the use of nonsteroidal anti-inflammatory drugs during menses throughout the study
Use of medication intended for treatment of DUB symptoms (eg, tranexamic acid)
Hormonal contraception: • OCs or intravaginal contraception within 30 days of Visit 1 • IUD still in place within 30 days of Visit 1 • Implants/depots still in place within 30 days of Visit 1 • Intramuscular: visit 1 less than 30 days from the last day of the labeled effective period of use
Use of steroidal OC agents during the study
Concomitant use of medication inhibiting or inducing cytochrome CYP 3A4 and continuous systemic use of antibiotics were excluded
Any concomitant or active disease or condition that compromised the absorption, distribution, metabolism, or excretion of the study drug (such as compromised renal function, gastrectomy, pancreatitis, renal insufficiency, hepatic dysfunction, active cholecystitis, and cholestatic jaundice)
Known or suspected premalignant or malignant disease including malignant melanoma (excluding other successfully treated skin cancers) or a history of these conditions
Abnormal laboratory values that were considered clinically significant at the discretion of the investigator and which gave suspicion of a specific organ or system dysfunction
History of myocardial infarction or coronary heart disease requiring treatment
History of congestive heart failure
Uncontrolled hypertension; sitting systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mm Hg
History of stroke or transient ischemic attacks
Vascular diseases: Presence or history of venous thromboembolic diseases (deep vein thrombosis, pulmonary embolism), presence or history of arterial thromboembolic diseases (myocardial infarction, stroke), and any condition that could increase the risk to suffer from any of the above mentioned disorders, e.g. a positive family history (event that occurred in a sibling or a parent at an early age) or a hereditary predisposition
Uncontrolled thyroid disorders
Known sickle cell anemia
Known, not adequately controlled diabetes mellitus or with vascular involvement
Current or history of migraines with focal neurological symptoms
Increased frequency or severity of headaches including migraines during previous estrogen therapy
History of drug addiction or alcohol abuse (within the last 2 years)
Current or history of clinically significant depression (hospitalization)
Known allergic reactions and/or hypersensitivity to EV, or DNG, or other ingredients of the study drug
Known allergic reactions and/or hypersensitivity to sanitary protection
Heavy smoker (more than 10 cigarettes per day) over the age of 35
BMI > 32 kg/m^2 calculated using the equation: body weight (kg)/[body height (m)]^2

The primary efficacy variable was the overall success rate, which was defined by the number of patients with the absence of any DUB symptom (as recorded in the e-Diary) and who have met all the relevant criteria for success during the 90-day efficacy assessment phase, as compared with the number of patients having at least one qualifying DUB symptom during the run-in phase. The secondary efficacy variables were the:

- Proportion of patients cured from each individual symptom
- Change in blood loss volume for all patients and for patients with excessive bleeding (menstrual blood loss was measured by the alkaline haematin method)

- Change in number of bleeding days and bleeding episodes
- Change in number of sanitary protection used
- Proportion of patients with improvement in the Investigator's Global Assessment scale at Days 84 and 196
- Proportion of patients with improvement in the Patient's Overall Assessment scale at Days 84 and 196
- Change from baseline in Quality of Life (QoL) scores at Days 84 and 196. The following QoL measures were used:
    - The Psychological General Well-Being Index (PGWBI)
    - The McCoy Female Sexuality Questionnaire (MFSQ)
    - The EuroQoL 5 Dimensional Health Questionnaire (EQ-5D)
- Resource use assessment at baseline, Days 84 and 196
- Change from baseline in hemoglobin and serum ferritin concentrations at Days 84 and 196

Absence of DUB symptoms was defined as:

- No bleeding episodes lasting more than seven days, and
- No more than four bleeding episodes, and
- No bleeding episodes with blood loss volume of 80 mL or more

In addition,

- No more than one bleeding episode increase from baseline, and
- Total number of bleeding days not to exceed 24 days
- No increase from baseline in an individual patient's total number of bleeding days.

In addition, for patients enrolled with specific symptoms, the following criteria had to be met:

- If patients enrolled with prolonged bleeding, the decrease between the maximum duration during run-in phase and the maximum duration during the efficacy phase was at least two days
- If patients enrolled with excessive bleeding: (1) the blood loss volume associated with each episode was <80 mL and (2) the blood loss volume associated with each bleeding episode represented a decrease of at least 50% from the average of the qualifying bleeding episodes, where the qualifying bleeding episodes were those with a blood loss volume of ≥80 mL (per episode) that occurred during the run-in phase

The following definitions were used for bleeding intensity:

- None = No vaginal bleeding
- Spotting = Less than associated with normal menstruation relative to the patient's experience with no need for sanitary protection (except for panty liners)
- Light = Less than associated with normal menstruation relative to the patient's experience with need for sanitary protection
- Normal = Like normal menstruation relative to the patient's experience
- Heavy = More than normal menstruation relative to the patient's experience

Statistical Analysis for Study 308960/A29849

Hypothesis tests were performed for the primary efficacy outcome measure using the difference in proportions and the corresponding unconditional two-sided 95% confidence interval. Secondary efficacy variables were tested using analysis of covariance (ANCOVA) models with baseline variables added as covariates.

The sample size calculation was based on:

- A ratio of 2:1 (EV/DNG: placebo)

- An assumption of a dropout rate of 30%
- A power of 90%
- A level of significance of 0.05
- An overall success rates in the EV/DNG group and the placebo group of 50% and 20%, respectively

Using these assumptions, 120 patients in the EV/DNG group and 60 patients in the placebo group (180 total) provided a power of 90% to test the null hypothesis that the proportions of success in the two treatment groups were equal, at a 5% significance level.

Results for Study 308960/A29849

A total of 1077 subjects were screened, 887 subjects failed screening and 190 subjects were randomised: 120 to EV/DNG and 70 to placebo. All subjects were female with an age range of 20 to 53 years. The treatment groups were similar in demographic, physical characteristics and DUB symptoms at baseline. However, a higher proportion of subjects in the EV/DNG group had irregular cycles at baseline. Two patients (both in the EV/DNG group) took progestogens or progestogens and oestrogens (fixed combinations) during the study. Use of iron preparations and iron bivalents (oral preparations) during the study was less frequent in the EV/DNG group than in the placebo group; two (1.7%) and twelve (10.1%) subjects respectively in the EV/DNG group; and four (6.1%) and eleven (16.7%) patients, respectively, in the placebo group.

For the primary efficacy outcome variable, there was a statistically and clinically significant improvement with EV/DNG: the difference in the proportion of responders between treatment groups was 0.2631, p <0.0001, Odds Ratio (OR) (95% Confidence Intervals [CI]) 13.417 (3.1240 to 57.626) (Table 3). However, around 70% of the EV/DNG group were non-responders.

Table 3: Responder Analysis for Overall DUB Symptoms by Treatment (intent to treat [ITT] population)

	EV/DNG (N = 120)	Placebo (N = 70)	
Responder [a]	35 (29.17%)	2 (2.86%)	
Nonresponder	85 (70.83%)	68 (97.14%)	
Proportion of responders	0.2917	0.0286	
Difference (EV/DNG-placebo)			0.2631
P-value [b]			<.0001
95% confidence limits [c]			0.1606,0.3573

[a] A responder is defined as having no DUB symptoms in the 90-day efficacy phase.[3]
[b] Two-sided exact P-value was obtained from StatXact using binomial procedure.
[c] 95% two-sided exact confidence interval was obtained by converting 2 separate one-sided test of half the nominal significance level each.

For the secondary efficacy outcome variables:

- There were insufficient numbers of subjects with frequent bleeding (six) to detect a treatment difference
- There was a higher proportion of subjects in the Qlaira group with excessive bleeding that responded: 29 (44.62%) compared with two (4.76%) (Table 4)

Table 4: Responder Analysis for Responders/Non-responders (Symptomatic) for Overall DUB Symptoms for Patients who Enrolled with Excessive Bleeding by Treatment (ITT)

	EV/DNG (N = 65)	Placebo (N = 42)
Responder [a]	29 (44.62%)	2 (4.76%)
Nonresponder	36 (55.38%)	40 (95.24%)
95% confidence limits	0.3227, 0.5747	0.0058, 0.1616

[a] A responder is defined as having no DUB symptoms in the 90-day efficacy phase.

- There was a greater decrease from baseline in adjusted mean blood loss in the Qlaira group than in the placebo group: -368.22 mL compared with -116.37 mL; mean difference (95% CI) -251.85 (-339.20 to -164.50) mL, p-value <0.0001
- There was no significant difference between treatments in the number of bleeding episodes
- There was a greater decrease in number of sanitary protection items: mean (SD) -43.6 (40.90) for Qlaira and -21.1 (43.24) for placebo; mean difference (95% CI) -23.4 (-38.69 to -8.03). p <0.0001
- A greater proportion of subjects in the Qlaira group had an improvement in Investigator's Global Scale at Day 196: treatment difference (95% CI) 0.3877 (0.2369 to 0.5263) p-value <0.0001 (Table 5)

Table 5: Analysis of Proportion of Patients with Improvement in the Investigator's Global Assessment Scale (ITT)

		EV/DNG (N = 120)	Placebo (N = 70)	
Treatment day 84	Improved	88 (88.00%)	28 (50.91%)	
	Not improved	12 (12.00%)	27 (49.09%)	
	Proportion of improvement	0.8800	0.5091	
	Difference (EV/DNG-placebo)			0.3709
	P-value [a]			<.0001
	95% confidence limits [b]			0.2189,0.5165
Treatment day 196	Improved	92 (80.70%)	26 (41.94%)	
	Not improved	22 (19.30%)	36 (58.06%)	
	Proportion of improvement	0.8070	0.4194	
	Difference (EV/DNG-placebo)			0.3877
	P-value [a]			<.0001
	95% confidence limits [b]			0.2369,0.5263

[a] Two-sided exact P-value was obtained from StatXact using binomial procedure.
[b] 95% two-sided exact confidence interval was obtained by converting 2 separate one-sided test of half the nominal significance level each.

- A greater proportion of subjects in the Qlaira group had an improvement in Patient's Global Scale at Day 196: treatment difference (95% CI) 0.4288 (0.2529 to 0.5829) p-value <.0001 (Table 6)

Table 6: Analysis of Proportion of Patients with Improvement in the Patient's Overall Assessment Scale (ITT)

		EV/DNG (N = 120)	Placebo (N = 70)	
Treatment day 84	Improved	71 (83.53%)	20 (42.55%)	
	Not improved	14 (16.47%)	27 (57.45%)	
	Proportion of improvement	0.8353	0.4255	
	Difference (EV/DNG-placebo)			0.4098
	P-value [a]			<.0001
	95% confidence limits [b]			0.2320,0.5657
Treatment day 196	Improved	69 (81.18%)	18 (38.30%)	
	Not improved	16 (18.82%)	29 (61.70%)	
	Proportion of improvement	0.8118	0.3830	
	Difference (EV/DNG-placebo)			0.4288
	P-value [a]			<.0001
	95% confidence limits [b]			0.2529,0.5829

[a] Two-sided exact P-value was obtained from StatXact using binomial procedure.
[b] 95% two-sided exact confidence interval was obtained by converting 2 separate one-sided test of half the nominal significance level each.

- There was no difference between the treatment groups in PGWBI
- There was no difference between the treatment groups in MFSQ
- There was no difference between the treatment groups in EQ-5D
- From baseline to Day 196, there was an increase in haematocrit in the Qlaira group compared with placebo: mean difference (95% CI) 1.424 (0.558 to 2.290), p-value = 0.0014
- Serum ferritin improved in the Qlaira group compared with placebo, change from baseline to Day 196 was 2.916 ng/mL for Qlaira and -0.354 mg/mL for placebo, p = 0.0113
- There was a greater increase in haemoglobin (Hb) concentrations from baseline to Day 196 in the Qlaira group compared with placebo: 0.583 g/dL for Qlaira compared with 0.141 g/dL for control, p = 0.0042

Resource utilization was measured but statistical analysis and comparisons between groups do not appear to have been performed. There do not appear to be any significant differences between the groups. During the treatment phase there was little additional use of resources.

Study 308961/A42568

Study 308961/A42568 was a multicentre, double blind, randomised, parallel group, placebo controlled study of efficacy and safety of EV/DNG in subjects with DUB (Treatment of Prolonged, excessive, or frequent bleeding in women without organic pathology who desire oral contraception) (Table 7). The study was conducted at 34 centres in ten countries: Australia, Czech Republic, Finland, Germany, Hungary, The Netherlands, Poland, Sweden, UK and Ukraine.

The inclusion criteria were effectively identical to Study 308960/A29849 except for the requirements for mammography which were:

- For Czech Republic only: Current diagnosis or history of breast cancer
- For Australia and the UK only: Smoker over age of 35
- For UK only: body mass index >30 kg/m^2

Table 7: Study 308961/A42568

Number of subjects with age and sex	Diagnosis + criteria for inclusion/exclusion	Duration of Treatment	Test Product Dosage Regimen Route of administration, Formulation	Criteria for evaluation	Results (efficacy)	Adverse Reactions
575 subjects were screened and 231 were randomised: 149 to EV/DNG and 82 to placebo. A total of 117 subjects in the EV/DNG group and 65 in the placebo completed the study. All the study subjects were female and the age range of the subjects was 18 to 54 years.	As for Study 308960/ A29849: ≥18 years of age with DUB defined as at least one of the following symptoms within the 90-day run-in phase • Prolonged bleeding: 2 or more bleeding episodes • Frequent bleeding: greater than 5 bleeding episodes, with a minimum of 20 bleeding days overall • Excessive bleeding: 2 or more bleeding episodes each with blood loss volume of 80 mL or more Willing to use barrier contraception (eg, condoms) from screening through study completion Normal or clinically insignificant Pap smear results. Endometrial biopsy without evidence of malignancy or atypical hyperplasia	7 cycles of 28 days Treatment phase of 196 days duration Preceded by a 90 day run-in phase and followed by a follow-up phase of 30 days	Sequential regimen comprising 28 tablets per cycle taken in the following order: - 1 tablet daily containing 3.0 mg EV for 2 days - 1 tablet daily containing 2.0 mg EV+ 2.0 mg DNG for 5 days - 1 tablet daily containing 2.0 mg EV + 3.0 mg DNG for 17 days - 1 tablet daily containing 1.0 mg EV for 2 days - 1 tablet daily containing placebo for 2 days	The primary efficacy variable was the overall success rate, The secondary efficacy variables were the: Proportion of patients cured from each individual symptom Change in blood loss volume for all patients and for patients with excessive bleeding Change in number of bleeding days and bleeding episodes Change in number of sanitary protection used Proportion of patients with improvement in the Investigator's global assessment scale and in the patient's overall assessment scale	The difference (95% CI) in the proportion of responders between treatment groups was 0.2831 (0.1991 to 0.3650), and the OR (95% CI) for response was 27.258 (4.2604 to 174.40) p <0.0001. 70% of the EV/DNG group were non-responders. There was a higher proportion of subjects in the Qlaira group with excessive bleeding that responded. The change from baseline in adjusted mean blood loss was higher in the Qlaira group than in the placebo group. There was no significant difference between treatments in the number of bleeding episodes. There were fewer bleeding days in the EV/DNG group compared with placebo. There was a greater decrease from baseline in number of sanitary protection items in the Qlaira group. A greater proportion of subjects in the Qlaira group improved in Investigator's Global Scale and Patient's Global Scale at Day 196. There was a deterioration in some of the QoL scales in the EV/DNG group	306 TEAEs were reported in 94 (64.8%) subjects in the EV/DNG group and 150 in 49 (60.5%) in the placebo. The most frequently reported AEs were: headache, nasopharyngitis, breast tenderness, serum ferritin decreased and acne. 2 SAEs were reported in 2 subjects in the EV/DNG group (breast cancer in situ, chronic cholecystitis) and 4 in 2 subjects in the placebo group. No deaths were reported. 14 (9.7%) subjects in the EV/DNG group and 5 (6.2%) in the placebo withdrew because of AEs.

Statistical Analysis for Study 308961/A42568

The study treatments and outcome measures were the same as for Study 308960/A29849. The timing of study procedures was identical to Study 308960/A29849, except for a review of the biopsy results at Visit 4. The sample size calculation was performed in an identical manner to Study 308960/A29849.

Results for Study 308961/A42568

A total of 575 subjects were screened and 231 were randomised: 149 to EV/DNG and 82 to placebo. A total of 117 subjects in the EV/DNG group and 65 in the placebo completed the study. The age range of the subjects was 18 to 54 years. Demographic and physical characteristics, alcohol consumption and smoking status were similar for the two treatment groups. The treatment groups were similar in contraceptive history, menstrual history and DUB symptoms at baseline, number of births and prior abortions. Concomitant oral iron preparations were taken by 25 (17.2%) subjects in the EV/DNG group and 14 (17.3%) in the placebo; progestogens by three (2.1%)

subjects in the EV/DNG group and two (2.5%) in the placebo; and combined progestogen and oestrogen medicines were taken by one subject in each treatment group.

EV/DNG was superior to placebo for the primary efficacy outcome measure (Table 8). This finding was clinically significant. The difference (95% CI) in the proportion of responders between treatment groups was 0.2831 (0.1991 to 0.3650), and the OR (95% CI) for response was 27.258 (4.2604 to 174.40) p <0.0001. However, 70% of the EV/DNG group were non-responders.

Table 8: Responder analysis for overall DUB symptoms by treatment (ITT)

	EV/DNG (N = 149)	**Placebo** (N = 82)	
Responder [a]	44 (29.53%)	1 (1.22%)	
Non-responder	105 (70.47%)	81 (98.78%)	
Proportion of responders	0.2953	0.0122	
Difference (EV/DNG-placebo)			0.2831
P-value [b]			<.0001
95% confidence limits [c]			0.1991,0.3650

[a] A responder is defined as having no DUB symptoms in the 90-day efficacy phase[13].
[b] Two-sided exact P-value was obtained from StatXact using binomial procedure.
[c] 95% two-sided exact confidence interval was obtained by converting 2 separate one-sided test of half the nominal significance level each.

For the secondary efficacy outcome variables:

- No subjects with frequent bleeding were enrolled in the study
- There was a higher proportion of subjects in the Qlaira group with excessive bleeding that responded: 60 (44.12%) compared with one (1.32%) in the placebo group (Table 9)

Table 9: Analysis of proportion of patients cured from excessive bleeding (ITT)

	EV/DNG (N = 136)	**Placebo** (N = 76)	
Cured	60 (44.12%)	1 (1.32%)	
Not cured	76 (55.88%)	75 (98.68%)	
Proportion of responders	0.4412	0.0132	
Difference (EV/DNG-placebo)			0.4280
P-value [a]			<.0001
95% confidence limits [b]			0.3349,0.5172

[a] Two-sided exact P-value was obtained from StatXact using binomial procedure.
[b] 95% two-sided exact confidence interval was obtained by converting 2 separate one-sided test of half the nominal significance level each.

- There was no significant difference in proportion of subjects in the EV/DNG group with prolonged bleeding that responded: seven (35.00%) compared with one (10%) in the placebo group

- There was a greater decrease from baseline in adjusted mean blood loss in the Qlaira group than in the placebo group: -452.16 mL compared with -79.471 mL; mean difference (95% CI) -372.69 (-489.91 to -255.47) mL, p <0.0001
- There was no significant difference between treatments in the number of bleeding episodes
- There was a significant decrease in the number of bleeding days in the EV/DNG group compared with placebo group: -2.080 (-4.115 to -0.045) p = 0.0186
- There was a greater decrease from baseline in number of sanitary protection items used: mean (SD) 38.43 (30.00) for Qlaira and 16.52 (32.17) for placebo; mean difference (95% CI) -22.238 (-30.451 to -14.026) p <0.0001
- A greater proportion of subjects in the Qlaira group had an improvement in Investigator's Global Scale at Day 196: treatment difference (95% CI) 0.4522 (0.3250 to 0.5693) p-value <0.0001 (Table 10)

Table 10: Analysis of proportion of patients with improvement in the Investigator's Global Assessment Scale (ITT)

		EV/DNG (N = 149)	Placebo (N = 82)	
Treatment day 84	Improved	109 (83.85%)	28 (39.44%)	
	Not improved	21 (16.15%)	43 (60.56%)	
	Proportion of improvement	0.8385	0.3944	
	Difference (EV/DNG-placebo)			0.4441
	P-value [a]			**<.0001**
	95% confidence limits [b]			0.3078,0.5695
Treatment day 196	Improved	122 (84.72%)	32 (39.51%)	
	Not improved	22 (15.28%)	49 (60.49%)	
	Proportion of improvement	0.8472	0.3951	
	Difference (EV/DNG-placebo)			0.4522
	P-value [a]			**<.0001**
	95% confidence limits [b]			0.3250,0.5693

[a] Two-sided exact P-value was obtained from StatXact using binomial procedure.
[b] 95% two-sided exact confidence interval was obtained by converting 2 separate one-sided test of half the nominal significance level each.

- A greater proportion of subjects in the Qlaira group had an improvement in Patient's Global Scale at Day 196: treatment difference (95% CI) 0.3287 (0.1866 to 0.4613) p-value <0.0001 (Table 11)

Table 11: Analysis of Proportion of Patients with Improvement in the Patient's Overall Assessment Scale (ITT Set)

		EV/DNG (N = 149)	Placebo (N = 82)	
Treatment day 84	Improved	92 (72.44%)	36 (52.94%)	
	Not improved	35 (27.56%)	32 (47.06%)	
	Proportion of improvement	0.7244	0.5294	
	Difference (EV/DNG-placebo)			0.1950
	P-value [a]			**0.0080**
	95% confidence limits [b]			0.0504,0.3369
Treatment day 196	Improved	106 (77.94%)	32 (45.07%)	
	Not improved	30 (22.06%)	39 (54.93%)	
	Proportion of improvement	0.7794	0.4507	
	Difference (EV/DNG-placebo)			0.3287
	P-value [a]			**<.0001**
	95% confidence limits [b]			0.1866,0.4613

[a] Two-sided exact P-value was obtained from StatXact using binomial procedure.
[b] 95% two-sided exact confidence interval was obtained by converting 2 separate one-sided test of half the nominal significance level each.

- There was a significant decrease in PGWBI in the EV/DNG group compared with placebo
- There was no difference between the treatment groups in overall MFSQ but there was worsening for some of the subscales in the EV/DNG group compared to placebo
- There was no difference between the treatment groups in EQ-5D. However, in the visual analogue score there was a significant decrease in well being in the EV/DNG group compared with placebo.
- From baseline to Day 196, there was an increase in haematocrit in the Qlaira group compared with placebo: mean difference (95% CI) 1.559 (0.479 to 2.640) p=0.0049
- Serum ferritin improved in the Qlaira group compared with placebo, change from baseline to Day 196 was 8.624 ng/mL for Qlaira and 0.441 mg/mL for placebo, p = 0.0017
- There was a greater increase in Hb concentrations from baseline to Day 196 in the Qlaira group compared with placebo: 0.701 g/dL for Qlaira compared with 0.062 g/dL for control, p <0.0001

Resource utilization was measured but statistical analysis and comparisons between groups do not appear to have been performed.

Combined Reports of Efficacy for DUB

The Biometrical Report of Efficacy for DUB indicated that overall there was a large number of screening failures, predominantly for failing to meet inclusion criteria. There were also a high, but lower than originally planned, proportion of treatment discontinuations, with the most common reason being adverse effects (AEs) (Table 12).

Table 12: Premature Discontinuation from Study Medication by Treatment - Pooled and All Studies, ITT

	EV/DNG tablets pooled (N=269)	Placebo pooled (N=152)
Number of Subjects	269 (100.0%)	152 (100.0%)
Study medication		
study medication never administered	5 (1.9%)	5 (3.3%)
completed	193 (71.7%)	113 (74.3%)
prematurely discontinued	67 (24.9%)	32 (21.1%)
unknown	4 (1.5%)	2 (1.3%)
Reason for discontinuation from study medication		
missing	1 (0.4%)	1 (0.7%)
withdrawal of consent	21 (7.8%)	8 (5.3%)
protocol deviation	5 (1.9%)	3 (2.0%)
adverse event	26 (9.7%)	9 (5.9%)
pat. lost, no further information avail.	1 (0.4%)	3 (2.0%)
pregnancy	0 (0.0%)	2 (1.3%)
other	13 (4.8%)	6 (3.9%)

For the primary efficacy outcome measure, the combined analysis indicated similar response to the individual studies, with an OR (95% CI) of 20.659 (7.5260 to 85.392) p <0.0001 (Table 13).

Table 13: Responder Analysis for Overall DUB Symptoms by Treatment - Pooled Studies, ITT

	EV/DNG tablets (N=269)	Placebo (N=152)	
Responder* (n, %)	79 (29.37%)	3 (1.97 %)	
Non Responder (n, %)	190 (70.63%)	149 (98.03%)	
Proportion of Responders	0.2937	0.0197	
Difference (EV/DNG-Placebo)		.	0.2739
P-value [1]		.	<.0001
95% confidence Limits [2]	.	.	0.2123,0.3347

Overall there were insufficient subjects with prolonged bleeding to demonstrate efficacy for this subgroup. There were also insufficient subjects with frequent bleeding to demonstrate efficacy for this subgroup. However, efficacy was demonstrated for the subgroup of subjects with excessive bleeding (Table 14).

Table 14: Analysis of Proportion of Subjects Cured From Excessive Bleeding DUB Symptom - Pooled Studies, ITT

	EV/DNG tablets (N=227)	Placebo (N=136)	
Cured (n, %)	95 (41.85%)	4 (2.94 %)	
Not cured (n, %)	132 (58.15%)	132 (97.06%)	
Proportion of Responders	0.4185	0.0294	
Difference (EV/DNG-Placebo)		.	0.3891
P-value [1]		.	<.0001
95% confidence Limits [2]	.	.	0.3156,0.4597

EV/DNG was superior to placebo for both the Investigator's Global Response Scale and the Patient's Global Response Scale at Day 84 and Day 196 (Tables 15 and 16).

Table 15: Analysis of Proportion of Subjects with Improvement in the Investigator's Global Assessment Scale by Treatment and Time point - Pooled Studies, ITT

Timepoint		EV/DNG tablets (N=269)	Placebo (N=152)	
Treatment Day 84	Improve (n, %)	197 (85.65%)	56 (44.44%)	
	Not Improve (n, %)	33 (14.35%)	70 (55.56%)	
	Proportion of Improvement	0.8565	0.4444	
	Difference (EV/DNG-Placebo)		.	0.4121
	P-value [1]		.	<.0001
	95% confidence Limits [2]	.	.	0.3120,0.5082
Treatment Day 196	Improve (n, %)	214 (82.95%)	58 (40.56%)	
	Not Improve (n, %)	44 (17.05%)	85 (59.44%)	
	Proportion of Improvement	0.8295	0.4056	
	Difference (EV/DNG-Placebo)		.	0.4239
	P-value [1]		.	<.0001
	95% confidence Limits [2]	.	.	0.3280,0.5145

Table 16: Analysis of Proportion of Subjects with Improvement in the Subject's Overall Assessment Scale by Treatment and Time point - Pooled Studies, ITT

Timepoint		EV/DNG tablets (N=269)	Placebo (N=152)	
Treatment Day 84	Improve (n, %)	163 (76.89%)	56 (48.70%)	
	Not Improve (n, %)	49 (23.11%)	59 (51.30%)	
	Proportion of Improvement	0.7689	0.4870	
	Difference (EV/DNG-Placebo)		.	0.2819
	P-value [1]		.	<.0001
	95% confidence Limits [2]	.	.	0.1721,0.3887
Treatment Day 196	Improve (n, %)	175 (79.19%)	50 (42.37%)	
	Not Improve (n, %)	46 (20.81%)	68 (57.63%)	
	Proportion of Improvement	0.7919	0.4237	
	Difference (EV/DNG-Placebo)		.	0.3681
	P-value [1]		.	<.0001
	95% confidence Limits [2]	.	.	0.2611,0.4703

From baseline to efficacy phase, the adjusted mean blood loss deceased to a greater extent in the EV/DNG group: -409.75 mL compared with -105.81 mL in the placebo group; mean difference (95% CI) -303.94 (-387.25 to -220.63) mL, p <0.0001. The number of bleeding days decreased to a greater extent in the EV/DNG group: adjusted mean -5.122 days, compared with -2.599 days for the placebo group; mean difference (95% CI) -2.523 (-4.772 to -0.274) days, p = 0.0038. The number of sanitary protection items used decreased to a greater extent in the EV/DNG group: adjusted mean -41.007 items compared with -18.858 items for the placebo group; adjusted mean difference (95% CI) -22.149 (-30.720 to -13.579) items, p <0.0001.

There was no difference in PGWBI score for anxiety, positive well-being, health change, vitality or total score. There was a marginal decrease in PGWBI depressed mood score in the EV/DNG group compared with placebo: adjusted mean difference (95% CI) -0.478 (-0.897 to -0.059), p = 0.0433. There was a marginal decrease in PGWBI self control score in the EV/DNG group compared with placebo: adjusted mean difference (95% CI) -0.647 (-1.155 to -0.138), p = 0.0193. There was a decrease in the MFSQ sexual interest score in the EV/DNG group relative to placebo: adjusted mean difference (95% CI) -1.403 (-2.472 to -0.333), p = 0.0312. There was a decrease in the MFSQ lubrication score in the EV/DNG group relative to placebo: adjusted mean difference (95% CI) -1.058 (-1.817 to -0.299), p = 0.0017. There was a decrease in the EV/DNG group relative to placebo in the MFSQ score for orgasm: adjusted mean difference (95% CI) -1.362 (-2.325 to -0.400), p = 0.0124. There was no difference between the groups in MFSQ score for satisfaction, attractiveness or sex partner change. At Day 84, total MFSQ score was worse in the EV/DNG group but not at Day 196. There was no difference between the groups in EQ-5D Valuation score or Health Status Visual Analogue Scale.

There was an improvement in serum ferritin concentrations in the EV/DNG group relative to placebo. There was an improvement in Hb concentrations relative to placebo. At Day 196 there

was an improvement in haematocrit in the EV/DNG group relative to placebo: adjusted mean difference (95% CI) 1.399 (0.657 to 2.141), p = 0.0002.

In addition to the responder/non-responder analysis in the ITT population as displayed in Table 8, a responder/non-responder analysis in the ITT excluding study subjects with missing data was performed, i.e. only the proportion of responders and symptomatic non-responders was calculated. In this analysis the proportion of responders increased to 42.02%.

Safety

Introduction

Safety data for the indication of DUB were provided in the form of the two clinical study reports (Study 308960/A29849 and Study 308961/A42568) and also a pooled safety report comprising tabulations of data from the two clinical studies.

Patient Exposure

In Study 308960/A29849 summarised in Table 1, 118 subjects were treated with EV/DNG for a mean (SD) duration of 162.7 (60.25) days, median (range) 195 (10 to 221) days.

In Study 308961/A42568 summarised in Table 7, 144 subjects were treated with EV/DNG for a mean (SD) duration of 172.4 (49.44) days, median (range) 196.0 (21 to 204) days.

The Biometrical Report of Safety for DUB indicates that in total 164 subjects were treated with EV/DNG for 4 to 7 cycles and 64 for more than 7 cycles.

Adverse Events

In Study 308960/A29849, treatment-emergent adverse effects (TEAEs) were reported in 80 (67.2%) subjects in the EV/DNG group and 36 (54.5%) in the placebo group (Table 17). The most commonly reported TEAEs in the EV/DNG group were nasopharyngitis, acne, metrorrhagia, nausea, and bacterial vaginitis. There were no significant differences between the treatment groups in vital signs. There were four pregnancies, all occurring in the placebo group.

Table 17: TEAEs reported in Study 308960/A29849

System Organ Class/Preferred Term	Placebo Events	Placebo N=66 (100%)	EV/DNG Events	EV/DNG N=119 (100%)	Total Events	Total N=185 (100%)
ANY EVENT	134	36 (54.5%)	230	80 (67.2%)	364	116 (62.7%)
Blood and lymphatic system disorders						
ANY EVENT	4	4 (6.1%)	4	3 (2.5%)	8	7 (3.8%)
Anaemia	4	4 (6.1%)	3	2 (1.7%)	7	6 (3.2%)
Lymphadenopathy	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Cardiac disorders						
ANY EVENT	1	1 (1.5%)	1	1 (0.8%)	2	2 (1.1%)
Myocardial infarction	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Tachycardia	1	1 (1.5%)	0	0 (0.0%)	1	1 (0.5%)
Ear and labyrinth disorders						
ANY EVENT	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Hyperacusis	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Endocrine disorders						
ANY EVENT	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Basedow's disease	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Eye disorders						
ANY EVENT	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Eye swelling	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Gastrointestinal disorders						
ANY EVENT	12	8 (12.1%)	24	16 (13.4%)	36	24 (13.0%)
Abdominal distension	1	1 (1.5%)	1	1 (0.8%)	2	2 (1.1%)
Abdominal pain	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Anal fistula	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Diarrhoea	2	2 (3.0%)	4	3 (2.5%)	6	5 (2.7%)
Dry mouth	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Dyspepsia	0	0 (0.0%)	3	3 (2.5%)	3	3 (1.6%)
Flatulence	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Nausea	6	5 (7.6%)	8	6 (5.0%)	14	11 (5.9%)
Stomach discomfort	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Umbilical hernia	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Vomiting	3	2 (3.0%)	2	2 (1.7%)	5	4 (2.2%)
General disorders and administration site conditions						
ANY EVENT	6	6 (9.1%)	8	7 (5.9%)	14	13 (7.0%)
Chest pain	2	2 (3.0%)	1	1 (0.8%)	3	3 (1.6%)
Fatigue	3	3 (4.5%)	4	4 (3.4%)	7	7 (3.8%)
Influenza like illness	1	1 (1.5%)	0	0 (0.0%)	1	1 (0.5%)
Oedema peripheral	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Pyrexia	0	0 (0.0%)	2	1 (0.8%)	2	1 (0.5%)
Immune system disorders						
ANY EVENT	2	2 (3.0%)	1	1 (0.8%)	3	3 (1.6%)
Allergy to animal	1	1 (1.5%)	0	0 (0.0%)	1	1 (0.5%)
Seasonal allergy	1	1 (1.5%)	1	1 (0.8%)	2	2 (1.1%)
Infections and infestations						
ANY EVENT	27	22 (33.3%)	59	36 (30.3%)	86	58 (31.4%)
Abscess jaw	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Bronchitis	2	2 (3.0%)	4	3 (2.5%)	6	5 (2.7%)
Cellulitis	2	1 (1.5%)	0	0 (0.0%)	2	1 (0.5%)
Ear infection	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Fungal infection	1	1 (1.5%)	2	2 (1.7%)	3	3 (1.6%)
Furuncle	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Gastroenteritis	0	0 (0.0%)	4	3 (2.5%)	4	3 (1.6%)
Influenza	0	0 (0.0%)	3	3 (2.5%)	3	3 (1.6%)
Kidney infection	1	1 (1.5%)	0	0 (0.0%)	1	1 (0.5%)
Nasopharyngitis	7	6 (9.1%)	9	9 (7.6%)	16	15 (8.1%)
Oral herpes	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Pharyngitis streptococcal	1	1 (1.5%)	1	1 (0.8%)	2	2 (1.1%)
Pilonidal cyst	1	1 (1.5%)	0	0 (0.0%)	1	1 (0.5%)
Pneumonia	0	0 (0.0%)	2	2 (1.7%)	2	2 (1.1%)
Sinusitis	1	1 (1.5%)	4	4 (3.4%)	5	5 (2.7%)
Tooth abscess	1	1 (1.5%)	1	1 (0.8%)	2	2 (1.1%)
Upper respiratory tract	1	1 (1.5%)	5	4 (3.4%)	6	5 (2.7%)
Urinary tract infection	0	0 (0.0%)	2	2 (1.7%)	2	2 (1.1%)
Vaginal candidiasis	1	1 (1.5%)	0	0 (0.0%)	1	1 (0.5%)
Vaginal infection	0	0 (0.0%)	4	3 (2.5%)	4	3 (1.6%)
Vaginitis bacterial	4	4 (6.1%)	7	6 (5.0%)	11	10 (5.4%)
Viral infection	1	1 (1.5%)	0	0 (0.0%)	1	1 (0.5%)
Vulvovaginal mycotic infection	3	3 (4.5%)	7	4 (3.4%)	10	7 (3.8%)

System Organ Class/Preferred Term	Placebo Events	Placebo N=66 (100%)	EV/DNG Events	EV/DNG N=119 (100%)	Total Events	Total N=185 (100%)
Musculoskeletal and connective tissue disorders						
ANY EVENT	11	6 (9.1%)	11	9 (7.6%)	22	15 (8.1%)
Arthralgia	3	3 (4.5%)	0	0 (0.0%)	3	3 (1.6%)
Back pain	3	3 (4.5%)	3	3 (2.5%)	6	6 (3.2%)
Bursitis	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Flank pain	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Muscle spasms	1	1 (1.5%)	1	1 (0.8%)	2	2 (1.1%)
Musculoskeletal pain	1	1 (1.5%)	1	1 (0.8%)	2	2 (1.1%)
Musculoskeletal stiffness	1	1 (1.5%)	0	0 (0.0%)	1	1 (0.5%)
Myalgia	2	1 (1.5%)	2	2 (1.7%)	4	3 (1.6%)
Neck pain	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Plantar fasciitis	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
ANY EVENT	0	0 (0.0%)	2	2 (1.7%)	2	2 (1.1%)
Skin papilloma	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Uterine leiomyoma	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Nervous system disorders						
ANY EVENT	34	11 (16.7%)	21	14 (11.8%)	55	25 (13.5%)
Dizziness	2	2 (3.0%)	0	0 (0.0%)	2	2 (1.1%)
Headache	28	9 (13.6%)	6	5 (4.2%)	34	14 (7.6%)
Hypoaesthesia	3	2 (3.0%)	1	1 (0.8%)	4	3 (1.6%)
Migraine	0	0 (0.0%)	4	3 (2.5%)	4	3 (1.6%)
Paraesthesia	1	1 (1.5%)	0	0 (0.0%)	1	1 (0.5%)
Presyncope	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Sinus headache	0	0 (0.0%)	4	2 (1.7%)	4	2 (1.1%)
Tension headache	0	0 (0.0%)	5	4 (3.4%)	5	4 (2.2%)
Psychiatric disorders						
ANY EVENT	7	4 (6.1%)	15	11 (9.2%)	22	15 (8.1%)
Affect lability	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Anxiety	3	3 (4.5%)	1	1 (0.8%)	4	4 (2.2%)
Bruxism	0	0 (0.0%)	2	1 (0.8%)	2	1 (0.5%)
Crying	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Depression	1	1 (1.5%)	4	3 (2.5%)	5	4 (2.2%)
Emotional disorder	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Insomnia	2	2 (3.0%)	1	1 (0.8%)	3	3 (1.6%)
Libido decreased	0	0 (0.0%)	2	2 (1.7%)	2	2 (1.1%)
Mood swings	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Orgasm abnormal	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Suicide attempt	1	1 (1.5%)	0	0 (0.0%)	1	1 (0.5%)

System Organ Class/Preferred Term	Placebo Events	Placebo N=66 (100%)	EV/DNG Events	EV/DNG N=119 (100%)	Total Events	Total N=185 (100%)
Renal and urinary disorders						
ANY EVENT	1	1 (1.5%)	1	1 (0.8%)	2	2 (1.1%)
Nephrolithiasis	1	1 (1.5%)	0	0 (0.0%)	1	1 (0.5%)
Urinary tract pain	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Reproductive system and breast disorders						
ANY EVENT	16	8 (12.1%)	41	29 (24.4%)	57	37 (20.0%)
Breast discharge	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Breast enlargement	1	1 (1.5%)	0	0 (0.0%)	1	1 (0.5%)
Breast pain	0	0 (0.0%)	7	5 (4.2%)	7	5 (2.7%)
Breast tenderness	1	1 (1.5%)	4	4 (3.4%)	5	5 (2.7%)
Cervical dysplasia	2	2 (3.0%)	3	3 (2.5%)	5	5 (2.7%)
Cervical polyp	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Cervix erythema	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Cystocele	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Dysmenorrhoea	8	2 (3.0%)	3	3 (2.5%)	11	5 (2.7%)
Genital discharge	1	1 (1.5%)	1	1 (0.8%)	2	2 (1.1%)
Menorrhagia	0	0 (0.0%)	2	2 (1.7%)	2	2 (1.1%)
Menstrual disorder	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Metrorrhagia	0	0 (0.0%)	7	6 (5.0%)	7	6 (3.2%)
Nipple disorder	1	1 (1.5%)	0	0 (0.0%)	1	1 (0.5%)
Ovulation pain	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Pelvic discomfort	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Pelvic pain	1	1 (1.5%)	1	1 (0.8%)	2	2 (1.1%)
Premenstrual syndrome	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Uterine cervical erosion	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Uterine haemorrhage	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Vaginal discharge	1	1 (1.5%)	2	2 (1.7%)	3	3 (1.6%)
Vulvovaginal pruritus	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Respiratory, thoracic and mediastinal disorders						
ANY EVENT	4	2 (3.0%)	6	5 (4.2%)	10	7 (3.8%)
Allergic sinusitis	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Asthma	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Cough	1	1 (1.5%)	1	1 (0.8%)	2	2 (1.1%)
Dyspnoea	2	1 (1.5%)	0	0 (0.0%)	2	1 (0.5%)
Nasal congestion	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Paranasal sinus hypersecretion	1	1 (1.5%)	0	0 (0.0%)	1	1 (0.5%)
Pharyngolaryngeal pain	0	0 (0.0%)	2	2 (1.7%)	2	2 (1.1%)
Skin and subcutaneous tissue disorders						
ANY EVENT	2	2 (3.0%)	17	12 (10.1%)	19	14 (7.6%)
Acne	0	0 (0.0%)	6	6 (5.0%)	6	6 (3.2%)
Blister	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Dermatitis allergic	1	1 (1.5%)	0	0 (0.0%)	1	1 (0.5%)
Dermatitis contact	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Dry skin	0	0 (0.0%)	2	2 (1.7%)	2	2 (1.1%)
Eczema	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Erythema	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Ingrowing nail	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Pityriasis rosea	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Rash	1	1 (1.5%)	2	2 (1.7%)	3	3 (1.6%)
Skin irritation	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Surgical and medical procedures						
ANY EVENT	0	0 (0.0%)	3	3 (2.5%)	3	3 (1.6%)
Endodontic procedure	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Neurectomy	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Tooth extraction	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Vascular disorders						
ANY EVENT	4	3 (4.5%)	3	3 (2.5%)	7	6 (3.2%)
Hot flush	0	0 (0.0%)	1	1 (0.8%)	1	1 (0.5%)
Hypertension	2	2 (3.0%)	2	2 (1.7%)	4	4 (2.2%)
Pallor	2	1 (1.5%)	0	0 (0.0%)	2	1 (0.5%)

In Study 308961/A42568, 306 TEAEs were reported in 94 (64.8%) subjects in the EV/DNG group and 150 in 49 (60.5%) in the placebo group. The most frequently reported AEs were headache, nasopharyngitis, breast tenderness, serum ferritin decreased and acne (Table 18). There were no significant differences between the treatment groups in vital signs. There were two pregnancies, both in the placebo group.

Table 18: Number (%) of Patients with Treatment-Emergent Adverse Events (occurring in >1% of the EV/DNG group) by Preferred Term and Descending Frequency of Total Patients

	Placebo		EV/DNG		Total	
Preferred Term	Events	N=81 (100%)	Events	N=145 (100%)	Events	N=226 (100%)
Any Event	150	49 (60.5%)	306	94 (64.8%)	456	143 (63.3%)
Headache	23	11 (13.6%)	46	21 (14.5%)	69	32 (14.2%)
Nasopharyngitis	4	4 (4.9%)	15	12 (8.3%)	19	16 (7.1%)
Breast tenderness	4	3 (3.7%)	6	6 (4.1%)	10	9 (4.0%)
Serum ferritin decreased	6	6 (7.4%)	3	3 (2.1%)	9	9 (4.0%)
Acne	3	3 (3.7%)	5	5 (3.4%)	8	8 (3.5%)
Breast pain	0	0 (0.0%)	10	8 (5.5%)	10	8 (3.5%)
Metrorrhagia	1	1 (1.2%)	8	7 (4.8%)	9	8 (3.5%)
Nausea	1	1 (1.2%)	7	7 (4.8%)	8	8 (3.5%)
Back pain	5	4 (4.9%)	3	3 (2.1%)	8	7 (3.1%)
Vomiting	5	4 (4.9%)	3	3 (2.1%)	8	7 (3.1%)
Abdominal pain	3	2 (2.5%)	7	4 (2.8%)	10	6 (2.7%)
Dysmenorrhoea	3	2 (2.5%)	5	4 (2.8%)	8	6 (2.7%)
Gamma-glutamyltransferase increased	3	3 (3.7%)	3	3 (2.1%)	6	6 (2.7%)
Viral infection	0	0 (0.0%)	6	6 (4.1%)	6	6 (2.7%)
Abdominal pain lower	8	2 (2.5%)	4	3 (2.1%)	12	5 (2.2%)
Fatigue	1	1 (1.2%)	4	4 (2.8%)	5	5 (2.2%)
Menorrhagia	4	4 (4.9%)	1	1 (0.7%)	5	5 (2.2%)
Migraine	3	2 (2.5%)	3	3 (2.1%)	6	5 (2.2%)
Pharyngitis	5	4 (4.9%)	1	1 (0.7%)	6	5 (2.2%)
Toothache	1	1 (1.2%)	5	4 (2.8%)	6	5 (2.2%)
Arthralgia	1	1 (1.2%)	3	3 (2.1%)	4	4 (1.8%)
Aspartate aminotransferase increased	1	1 (1.2%)	3	3 (2.1%)	4	4 (1.8%)
Blood pressure increased	0	0 (0.0%)	4	4 (2.8%)	4	4 (1.8%)
Hypertension	1	1 (1.2%)	3	3 (2.1%)	4	4 (1.8%)
Influenza	1	1 (1.2%)	3	3 (2.1%)	4	4 (1.8%)
Smear cervix abnormal	1	1 (1.2%)	3	3 (2.1%)	4	4 (1.8%)
Vaginal candidiasis	1	1 (1.2%)	4	3 (2.1%)	5	4 (1.8%)
Vulvovaginitis	0	0 (0.0%)	4	4 (2.8%)	4	4 (1.8%)
Abdominal distension	1	1 (1.2%)	2	2 (1.4%)	3	3 (1.3%)
Anaemia	1	1 (1.2%)	2	2 (1.4%)	3	3 (1.3%)
Breast discomfort	0	0 (0.0%)	3	3 (2.1%)	3	3 (1.3%)
Bronchitis	0	0 (0.0%)	3	3 (2.1%)	3	3 (1.3%)
Depressed mood	2	2 (2.5%)	1	1 (0.7%)	3	3 (1.3%)
Diarrhoea	2	1 (1.2%)	2	2 (1.4%)	4	3 (1.3%)
Haemoglobin decreased	1	1 (1.2%)	2	2 (1.4%)	3	3 (1.3%)
Libido decreased	1	1 (1.2%)	2	2 (1.4%)	3	3 (1.3%)
Mood altered	1	1 (1.2%)	2	2 (1.4%)	3	3 (1.3%)
Pharyngolaryngeal pain	2	2 (2.5%)	1	1 (0.7%)	3	3 (1.3%)
Pneumonia	0	0 (0.0%)	3	3 (2.1%)	3	3 (1.3%)
Sinusitis	2	2 (2.5%)	1	1 (0.7%)	3	3 (1.3%)
Urinary tract infection	2	2 (2.5%)	1	1 (0.7%)	3	3 (1.3%)
Vertigo	3	3 (3.7%)	0	0 (0.0%)	3	3 (1.3%)
Weight increased	1	1 (1.2%)	2	2 (1.4%)	3	3 (1.3%)
Alanine aminotransferase increased	0	0 (0.0%)	2	2 (1.4%)	2	2 (0.9%)
Asthma	1	1 (1.2%)	1	1 (0.7%)	2	2 (0.9%)
Breast enlargement	1	1 (1.2%)	1	1 (0.7%)	2	2 (0.9%)
Constipation	1	1 (1.2%)	1	1 (0.7%)	2	2 (0.9%)
Haematocrit decreased	0	0 (0.0%)	2	2 (1.4%)	2	2 (0.9%)
Hot flush	1	1 (1.2%)	1	1 (0.7%)	2	2 (0.9%)
Insomnia	0	0 (0.0%)	2	2 (1.4%)	2	2 (0.9%)
Iron deficiency anaemia	1	1 (1.2%)	1	1 (0.7%)	2	2 (0.9%)
Lower respiratory tract infection	0	0 (0.0%)	2	2 (1.4%)	2	2 (0.9%)
Mood swings	0	0 (0.0%)	2	2 (1.4%)	2	2 (0.9%)
Muscle spasms	1	1 (1.2%)	1	1 (0.7%)	2	2 (0.9%)
Oedema peripheral	0	0 (0.0%)	2	2 (1.4%)	2	2 (0.9%)
Pelvic pain	0	0 (0.0%)	2	2 (1.4%)	2	2 (0.9%)
Pruritus generalised	0	0 (0.0%)	2	2 (1.4%)	2	2 (0.9%)
Pyrexia	0	0 (0.0%)	3	2 (1.4%)	3	2 (0.9%)

The Biometrical Report did not provide additional insights into AEs in general.

Serious Adverse Events and Deaths

In Study 308960/A29849, two patients (1.1%) experienced treatment-emergent serious adverse events (SAEs); one each in the EV/DNG (myocardial infarction) and placebo (suicide attempt) groups.

In Study 308961/A42568, two SAEs were reported in two subjects in the EV/DNG group (breast cancer in situ, chronic cholecystitis) and four in two subjects in the placebo group (vertigo/panic attack, spontaneous abortion/complication of pregnancy).

No deaths were reported during Study 308960/A29849 or Study 308961/A42568.

Laboratory Findings

In Study 308960/A29849, two subjects in the EV/DNG group and five in the placebo were reported with anaemia. Two subjects in the EV/DNG group were reported with elevated gamma-glutamyltransferase. Seven subjects in the EV/DNG group and six in the placebo had glycosuria on

urinalysis at some time during the study. In the EV/DNG group, 16 patients had abnormal cervical smears at the end of study (EOS) visit, of which four were clinically significant. In the placebo group, 13 patients had abnormal cervical smears at the EOS visit, of which two were clinically significant.

In Study 308961/A42568, there were no significant differences between the treatment groups in mean laboratory parameters. Two (1.4%) subjects in the EV/DNG group were reported with elevated alanine transferase (ALT) and three (2.1%) with elevated aspartate transferase. Four subjects in the EV/DNG group were diagnosed with an abnormal Pap smear compared to one in the placebo group.

The Biometrical Report indicated that there were similar findings for EV/DNG and placebo for transitions in cytological smear findings.

Discontinuation due to Adverse Events

In Study 308960/A29849, 15 (8.1%) subjects discontinued due to TEAEs: 11 (9.2%) subjects in the EV/DNG group and four (6.1%) in the placebo group. Two subjects in the EV/DNG group withdrew because of tension headache.

In Study 308961/A42568, 14 (9.7%) subjects in the EV/DNG group and five (6.2%) in the placebo withdrew because of AEs. In the EV/DNG group these AEs were predominantly AEs that could be attributed to treatment: for example migraine, nausea, ALT elevated, altered mood.

Summary of Safety

The AE profile of Qlaira for the indication of DUB represents low risk and the AE profile for this indication is similar to that for the indication of oral contraception. The AEs reported in the DUB studies did not indicate inclusion of subjects with organic causes of bleeding.

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a "list of questions" to the sponsor is generated.

Efficacy

Does the Sponsor have any data for efficacy of Qlaira compared to active comparator for the indication of DUB?

Clinical Summary and Conclusions

Clinical Aspects

The sponsor submitted two placebo controlled clinical trials in support of efficacy and safety for the indication of DUB. Although there is demonstrable efficacy compared with placebo there are still a high proportion of patients who do not respond. Hence, data demonstrating efficacy in comparison to active comparator would be extremely useful for prescribers.

Benefit Risk Assessment

Benefits

The data presented in the submission demonstrate efficacy of Qlaira compared with placebo for the indication of DUB. This response was clinically significant. There was a decrease in DUB symptoms and also an improvement in Hb and ferritin. However, 70% of subjects did not meet the definition of responder. There was also failure to meet the predefined threshold for the proportion of complete responders in the pooled analysis. This response rate is overall disappointing and it would be important for prescribers to be able to compare Qlaira with other available treatments in

order to make informed choices when prescribing. Unfortunately, the two efficacy studies were not designed with an active comparator arm.

The sponsor responded that complete responders had to satisfy a composite of up to eight individual criteria over an efficacy period of 90 days, which required that, in addition to an absence of previous symptoms, patients also had to show a defined improvement in their condition. To the sponsor's knowledge, no other studies have used such strict response criteria. Indeed, many of the non-responders in the current studies would have been considered treatment successes in previous studies that used menstrual blood loss (MBL) volume as the primary efficacy criteria and in clinical practice. There are no data available directly comparing the efficacy of Qlaira with an active comparator. The placebo-controlled design for the Qlaira studies was chosen and agreed upon with regulatory authorities, because no adequate comparator was globally available for the DUB indication as targeted, that is, treatment of prolonged, excessive or frequent menstrual bleeding in women without pathology who desire oral contraception. In several countries the following products have an approved indication in uterine bleeding disorder but are not oral contraceptives and did therefore not qualify as adequate comparators for the studies: LNG-IUS (Mirena), some progestogens, hormone therapy products, tranexamic acid, mefenamic acid and etamsylate.

The outcome measures relating to global satisfaction and those relating to QoL are conflicting. Whilst the global satisfaction scores were favourable to Qlaira, the QoL scores were not. In Study 308961/A42568 there was a decrease in QoL in the Qlaira group as measured by PGWBI and MFSQ and also in the EQ-5D visual analogue score. The combined analysis of efficacy also indicates decrease in QoL scores. This indicates that these outcome measures were measuring different qualities of the treatment.

Organic pathology was ruled out satisfactorily in the treatment group by using endometrial biopsy as an exclusion criterion, by screening biochemistry and by the use of the other exclusion criteria in the protocol. The terms frequent, excessive and prolonged bleeding were also clearly defined in the inclusion criteria.

The efficacy results were analysed by type of DUB (frequent, prolonged and excessive) but were not analysed by intensity of symptoms. Hence it is not clear whether subjects with more severe symptoms will respond to a greater or lesser extent. Similarly, there was no subgroup analysis by failure to improve. Hence it is not possible to identify from the data the population that would be unlikely to respond to treatment.

The response occurred early in treatment and was stable over the course of treatment. Hence, it would be possible to identify non-responders within a few treatment cycles and to direct patients to alternative treatment strategies.

Pooling of results across the DUB studies was appropriate because of the similar design of the two studies.

Risks

The AE profile of Qlaira for the indication of DUB represents low risk and the AE profile for this indication is similar to that for the indication of oral contraception. The AEs reported in the DUB studies did not indicate inclusion of subjects with organic causes of bleeding.

Balance

The risk-benefit assessment is in favour of Qlaira. There is demonstrable efficacy for well-defined endpoints. The benefit was clinically and statistically significant. There were few SAEs and no deaths reported in the clinical trials.

Conclusions

Qlaira should be approved for the additional indication:

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

Conditions for Registration

The evaluator recommended that the sponsor should undertake to conduct comparator controlled studies for the indication of DUB. The choice of comparator should be discussed with the TGA.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Medicines Safety Monitoring (OMSM).

The sponsor identified the following important potential risks:

- Preferential prescribing in high risk populations
- Venous thrombotic events (VTEs)
- Arterial thromboembolic events (ATEs)

For these routine pharmacovigilance (PhV) and risk minimisation activities were proposed.[1,2] It was indicated that an International Active Surveillance Study of Women Taking EV/DNG (INAS-EV) and a preferential prescribing study are to be undertaken as additional PhV activities. There was also reference to an education program for medical practitioners, consumers and sales personnel.

The following important identified / potential risks were identified:

- Cervical and breast cancer
- Benign and malignant liver tumours
- Pancreatitis if associated with hypertriglyceridaemia
- Small increases in blood pressure
- Angioedema
- Acute or chronic disturbances of liver function
- Crohn's disease and ulcerative colitis

It was indicated that routine PhV and risk minimisation were planned for these.

---

[1] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

[2] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

The OMSM reviewer noted that the information provided in the RMP was satisfactory and the post marketing PhV surveillance and drug utilisation studies were commended. However, there were gaps in the information provided. It was recognised that this may be related to the longstanding use of combined oral contraceptives and consequent comprehensive knowledge about these products.

There were also issues with the PhV and risk minimisation plans. These related to the lack of:

- Clarity about what constitutes PhV and risk minimisation;
- Timeframes and mechanisms for reporting of results from ongoing studies; and
- Information on the methodology of the drug utilisation study and how this will be encompassed in the surveillance study, presentation of the statistical analysis plan for INAS-EV to regulatory agencies, and the content and implementation of the education program in Australia.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in an application of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in an application of this type.

Clinical

Efficacy

Study A29849 was a multicentre, randomised, double blind placebo controlled study of the efficacy and safety of oestradiol valerate/dienogest (EV/DNG) in subjects with dysfunctional uterine bleeding (DUB). Of note, women with DUB, who desired oral contraception, were eligible to participate. DUB was defined as having at least one of the following symptoms within 90 day run-in phase;

- prolonged bleeding: two or more bleeding episodes, each lasting 8 or more days
- frequent bleeding: greater than five bleeding episodes, with a minimum of 20 bleeding days overall
- excessive bleeding: two or more bleeding episodes each with blood loss volume of 80 mL or more, as assessed by the alkaline haematin method

Exclusion criteria were comprehensive and included organic uterine bleeding, abnormal transvaginal ultrasound results, atypical hyperplasia and other significant medical morbidities.

Following the 90 day run-in period there was the treatment phase lasting 7 cycles of 28 days; this was followed by a 30 day follow up phase. Treatment was administered as per the PI instructions for Qlaira.

The primary efficacy variable was the overall success rate, defined as the percentage of patients with the absence of any DUB symptom (recorded in the e-dairy) and who have met all relevant criteria for success during the 90-day efficacy assessment phase. (This phase was defined as the last 90-day period during treatment which started on Day 1 of a 28 day treatment cycle). The responder analysis was an integrated assessment of up to eight individual outcome measures. It was stated in the sponsor's response that "in order to qualify as a responder, a subject had to achieve not only a pre-determined level of improvement from baseline for each individual symptom but also be completely cleared from any heavy, prolonged and frequent bleeding during the entire 90 days." The sponsor should define it its pre-ACPM response, the definition of 'complete clearance".

The results for the primary endpoint are shown in Table 3. The evaluator noted that the active treatment was superior to placebo for the primary outcome measure. The definition of an overall success of the study required that the proportion of successful responders in the active treatment arm be statistically significantly greater than that in the placebo arm and the point estimate for the proportion of successful responder in the active treatment arm be at least 50%.

In terms of secondary endpoints, statistical and clinical superiority were seen in relation to the following: excessive bleeding, mean blood loss, sanitary protection items, investigator global scale, patient global scale, haematocrit, ferritin, haemoglobin. No significant difference was seen in relation to frequent bleeds, specified questionnaires and well being indices.

Study A42568 was similar in design to the previous study. A total of 149 subjects were randomised to the active treatment and 82 to the placebo group. Efficacy results are described in Table 8.

The evaluator noted that the active treatment was superior to placebo for the primary outcome measure. In terms of the secondary endpoints, statistical superiority of EV/DNG was seen in relation to excessive bleeding, mean blood loss, number of bleeding days, number of sanitary protection items, investigators global scale, patients global scale. No difference was seen in subjects with prolonged bleeding, number of bleeding episodes, and in certain well being questionnaires.

The evaluator noted that in the combined efficacy analysis the overall primary outcome measure was in line with that reported in individual studies. Insufficient numbers in some subgroups meant that efficacy could not be demonstrated in relation to some endpoints, notably prolonged bleeding and frequent bleeding. However, in relation to excessive bleeding, statistical significance favouring the active treatment was seen. Statistical superiority was seen in relation to investigator and patient global scale; there was also a decrease in adjusted mean blood loss and number of bleeding days. Improvement in ferritin and haemoglobin levels was seen. Well being and other scores did not show a significant difference.

Safety

A total of 164 subjects were treated with EV/DNG for 4-7 cycles and 64 for more than 7 cycles. Treatment-related adverse events reported with active treatment were nausea, acne, breast tenderness and headache.

In relation to serious adverse events, there was one report of myocardial infarction, one report of breast cancer in situ and one report of chronic cholecystitis in the active treatment group. Laboratory findings did not reveal any unusual findings.

Overall conclusion of the evaluator

The evaluator noted that organic pathology was ruled out by undertaking endometrial biopsy. The data demonstrated superiority of active over placebo in terms of the primary criterion. However 70% of the ITT did not meet the criterion of responder. Pooling of data failed to meet predefined threshold for responders. In the opinion of the evaluator, a significant deficiency was that Qlaira has not been compared to other available treatments. The evaluator concluded that there was a favourable risk benefit profile for Qlaira for the proposed indication and it should be recommended for approval.

The sponsor's response to the clinical evaluation report

The sponsor emphasised that complete responders had to satisfy a composite of up to eight individual criteria over an efficacy period of 90 days, which required that, in addition to an absence of previous symptoms, patients also had to show a defined improvement in their condition. Many of the non-responders in the studies performed with Qlaira would have been considered treatment successes in previous studies that used MBL volume as the primary efficacy criteria and in clinical practice.

The sponsor attached a detailed response. Of note:

1) The sponsor has updated the PI in relation to the risk of VTE with combined oral contraceptive use. There is also a "large post-marketing safety study" to evaluate the risk of VTE with Qlaira that has been initiated by Bayer with the study report due in the last quarter of 2014.

2) The presentation of efficacy results in a population other than the ITT, that is, the draft PI states,

"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 42.02%".

The Delegate noted that individual studies and the pooled analyses resulted in the responder rate being approximately 29%. The sponsor's justification for the new point estimate (42%) was that the primary endpoint was a composite of up to eight individual outcome parameters. Some of these were recorded in electronic diaries. Technical problems with these entries meant that some patients could not enter the data properly resulting in a "non-responder" status. Due to this, there has been an "ITT analysis" without non-responders due to missing values - hence, the point estimate of 42.02%. The sponsor also stated that,

"Without the information on what had to be fulfilled in order to be regarded as 'completely cured', the clinical efficacy of Qlaira is underestimated by presenting those percentages and the clinical meaningfulness of treatment with Qlaira would be misinterpreted."

The Delegate commented that this statement was unacceptable. The PI should present the efficacy endpoints that were included in the study protocol. The absolute response rate is about 25 to 27%.

Risk Management Plan

Routine pharmacovigilance and risk minimisation are planned for recognised risks associated with oral contraceptives. Several recommendations were made by the evaluator in relation to undertaking and reporting pharmacovigilance measures. The concerns of the OMSM evaluator were addressed by the sponsor in its response to the RMP evaluation report.

Risk-Benefit Analysis

Delegate Considerations

The primary efficacy endpoint is an integrated assessment of up to eight individual outcomes. The sponsor mentions in its response that the criteria used to assess responder analysis have been "stringent". However, the data only demonstrate efficacy against placebo and it is seriously deficient in not using an active comparator. No cross study comparisons can be made because efficacy endpoints used in other studies are different. Despite this deficiency, this data set includes some evidence of efficacy and safety of Qlaira in subjects with dysfunctional uterine bleeding.

The Delegate recommended approval of Qlaira for:

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

Response from Sponsor

The sponsor noted that after 6 months of treatment the 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.

Furthermore, the placebo-controlled design for the Qlaira studies was chosen and agreed upon with regulatory authorities, particularly the MEB and the FDA, because no adequate comparator was globally available for the DUB indication as targeted, that is, treatment of prolonged, excessive or frequent menstrual bleeding in women without pathology who desire oral contraception.

The Delegate requested that the definition of 'complete clearance' be defined in the pre-ACPM response. The sponsor advised that complete responders had to satisfy a composite of up to eight individual criteria over an efficacy period of 90 days, which required that, in addition to an absence of previous symptoms, patients also had to show a defined improvement in their condition.

The following criteria had to be met to fulfil the definition of complete response/clearance:

- No bleeding episodes lasting more than seven days and

- No more than four bleeding episodes and

- No bleeding episodes with blood loss volume of 80 mL or more

In addition,

- No more than one bleeding episode increase from baseline and total number of bleeding days not to exceed 24 days and

- No increase from baseline in an individual patient's total number of bleeding days

Furthermore, for patients enrolled with specific symptoms, the following criteria had to be met:

- If patients enrolled with prolonged bleeding, the decrease between the maximum duration during run-in phase and the maximum duration during the efficacy phase was to be at least two days

- If patients enrolled with excessive bleeding:

1. The blood loss volume associated with each episode was to be < 80 mL and

2. The blood loss volume associated with each bleeding episode was to represent a decrease of at least 50% from the average of the qualifying bleeding episodes, where the qualifying bleeding episodes were those with a blood loss volume ≥ 80 mL (per episode) that occurred during the run-in phase.

The remainder of the sponsor's response discussed issues concerning the PI which are beyond the scope of this AusPAR.

Advisory Committee Considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended approval for an extension of indication to include:

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

In making this recommendation the ACPM noted the advice from the Delegate that the study design is seriously deficient as it did not use an active comparator, and that cross study comparisons were not possible due to different efficacy endpoints. However, the ACPM agreed with the Delegate that overall a positive risk benefit profile had been demonstrated for the extended indication, and supported the changes to the Production Information and Consumer Medicine Information as proposed by the Delegate.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Qlaira containing oestradiol valerate and dienogest indicated for:

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

Included among the conditions of approval was that the latest Risk Management Plan, as agreed with the Office of Product review TGA, must be implemented.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

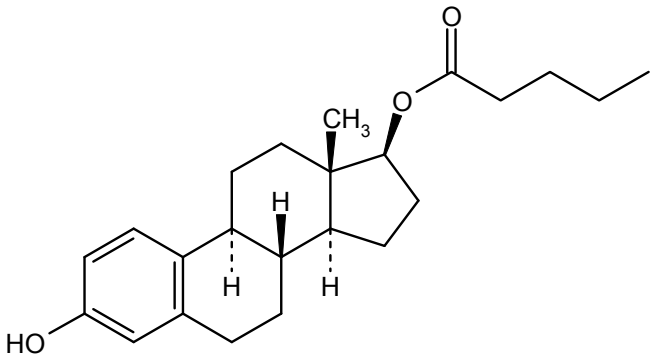
PRODUCT INFORMATION

QLAIRA® (oestradiol valerate / dienogest)

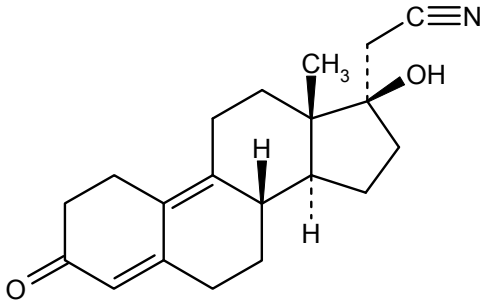
NAME OF THE MEDICINE

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-3,17β-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 oestradiol 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:



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 (0.05 mg ethinyloestradiol) 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 17β-oestradiol. The oestrogenic component used in this COC is therefore different from the oestrogens usually used in COCs which are the synthetic oestrogens ethinyloestradiol 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 ethinyloestradiol/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 85µg ^{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 ^{3}H-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 sulphates 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 QLAIRA. 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 QLAIRA was examined in three multi-center 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 (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 0.02mg 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 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% confidence limit 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.

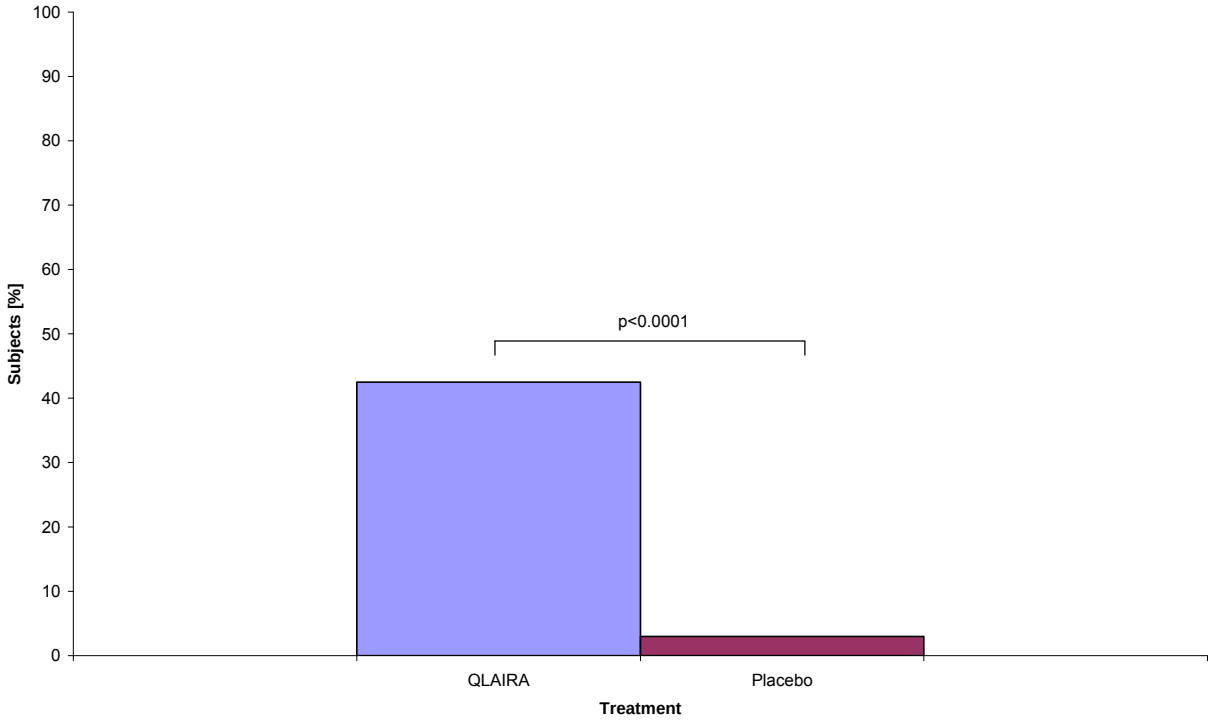
The safety profile of QLAIRA was not different from that of established low-dose COCs even though a considerable number of women older than 35 years of age were included in the clinical studies.

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 multi-center, 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.

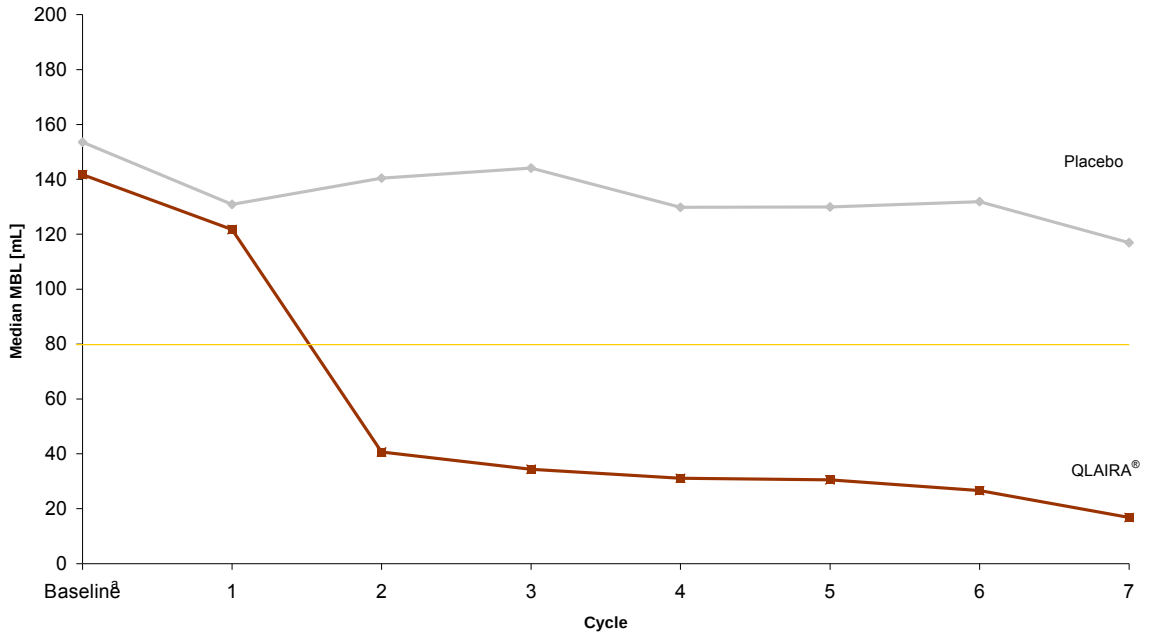
The primary efficacy variable was the proportion of subjects who were completely relieved of symptoms, which was defined by the number of subjects with the absence of any DUB symptom and who had met all the relevant criteria for success during the 90-day efficacy assessment phase. In both studies, QLAIRA was effective in treating the symptoms of dysfunctional uterine bleeding with a point estimate of the proportion of subjects with complete symptom relief of 29.37% in the QLAIRA group compared to 1.97% in the placebo group (difference 27.39%; CI of the difference 21.23% - 33.47%; $p<0.0001$). 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 42.02% (CI = 34.88% to 49.42%) in the QLAIRA group compared to 2.73% (CI = 0.57% to 7.76%) in the placebo group ($p<0.0001$) [see Figure 1].

Figure 1: Proportion of subjects completely relieved of DUB symptoms - pooled data from studies 308960/A29849 and 308961/A42568



Both studies demonstrated a clinically significant decrease in menstrual blood loss (MBL). In the QLAIRA group, the mean decrease in the 90-day efficacy phase compared to the 90-day run-in phase was 413.9 mL (SD 373.34). The decrease in the placebo group was 109.3mL (SD 299.59). The difference between the groups was statistically significant ($p<0.0001$, 95% CI = -387.25 to -220.63). 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). 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). Figure 2 display the median MBL volume by cycle based on pooled data from studies 308960/A29849 and 308961/A42568.

Figure 2: 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 change 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 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).

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 severe or multiple risk factor(s) for venous or arterial thrombosis (see **PRECAUTIONS** - **Circulatory disorders**)
- History of migraine with focal neurological symptoms
- Diabetes mellitus with vascular involvement
- Pancreatitis or a history thereof if associated with severe hypertriglyceridemia
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal
- Presence or history of liver tumours (benign or malignant)
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts)
- Undiagnosed vaginal bleeding
- 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.

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.

[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.

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 study[1] has shown that the frequency of VTE diagnosis ranges between 8 to 10 per 10,000 woman years in low estrogen 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 users[1], 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 accidents] 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 discolouration 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 heartbeat; 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. 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/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 COC use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilisation.

[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.

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 ethinyloestradiol).

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 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 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 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 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 **Advice 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 17β-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.

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 QLAIRA have been performed. However, studies have been performed for 17β-oestradiol and dienogest, the active components of QLAIRA.

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: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.

Interactions with other medicines

Effects of other medicinal products on QLAIRA

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

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 (MedDRA SOCs). Within each frequency grouping, undesirable effects are presented in order of decreasing frequency. Frequencies are

defined as common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and rare (1/10,000 to <1/1,000). All ADRs listed in the category 'rare' 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 (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥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 *one* tablet for more than 12 hours:**
1-2	**Dark yellow tablets** (3.0mg EV)	- 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)	- 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)	- 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)	- 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 **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 (131126) 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 Australia Limited
ABN 22 000 138 714
875 Pacific Highway
Pymble NSW 2073

POISON SCHEDULE OF THE MEDICINE:

PRESCRIPTION ONLY MEDICINE

DATE OF TGA APPROVAL:

Date of most recent amendment: 22 February 2010

® Registered Trademark of the Bayer Group, Germany