

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Qlaira, film-coated tablets
Bayer Schering AG, Germany**

estradiol valerate and dienogest

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.

It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

**EU-procedure number: NL/H/1230/001/DC
Registration number in the Netherlands: RVG 101491**

March 26th, 2009

Pharmacotherapeutic group:	progestogens and estrogens, sequential preparations
ATC code:	G03AB
Route of administration:	oral use
Therapeutic indication:	oral contraception
Prescription status:	prescription only
Date of authorisation in NL:	12 November 2008
Concerned Member States:	Decentralised procedure with AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, MT, NO, PL, PT, RO, SE, SI, SK, UK
Application type/legal basis:	Directive 2001/83/EC, Article 8(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Qlaira, film-coated tablets from Bayer Schering Pharma AG. The date of authorisation was on 12 November 2008 in the Netherlands. The product is indicated for oral contraception.

Each wallet for 28 days contains

- 2 tablets containing 3 mg estradiol valerate
- 5 tablets containing 2 mg estradiol valerate and 2 mg dienogest
- 17 tablets containing 2 mg estradiol valerate and 3 mg dienogest
- 2 tablets containing 1 mg estradiol valerate
- 2 tablets do not contain active substances

A comprehensive description of the indications and posology is given in the SPC.

The contraceptive effect of COCs is based on the interaction of various factors, the most important of which are seen as the inhibition of ovulation, changes in the cervical secretion, and changes in the endometrium.

The estrogen in Qlaira is estradiol valerate, an ester of the natural human 17 β -estradiol (1 mg estradiol valerate corresponds to 0.76 mg 17 β -estradiol). This estrogen differs from the estrogens ethinylestradiol or its prodrug mestranol used in all other COCs by the lack of an ethinyl group in 17 α position.

Dienogest is a nortestosterone derivative with no androgenic but rather an antiandrogenic activity of approximately one third of the same amount of that of cyproterone acetate. Dienogest binds to the progesterone receptor of the human uterus with only 10% of the relative affinity of progesterone. Despite its low affinity to the progesterone receptor, dienogest has a strong progestogenic effect in vivo. Dienogest has no significant androgenic, mineralocorticoid or glucocorticoid activity in vivo.

This decentralised procedure concerns a so-called full dossier application according to Article 8(3) of Directive 2001/83/EC, a dossier with administrative, chemical-pharmaceutical, pre-clinical and clinical data. Parts of these data were already submitted in the dossiers of the fixed combination of estradiol valerate 2 mg and dienogest 2 mg (Climodien, NL License RVG 24830) and the lower dosed medicinal product of estradiol valerate 1 mg and dienogest 2 mg (Climodien 1/2, NL License RVG 30401). However, these products are approved for another indication, i.e., hormone replacement therapy in postmenopausal women.

No scientific advice has been given to the MAH with respect to this product.

No paediatric development programme has been submitted.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

Active substances

General information

The active substances are estradiol valerate and dienogest. Estradiol valerate is described in the European Pharmacopoeia (Ph.Eur.), whereas dienogest is a well-known active substance, not described in a Pharmacopoeia. Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Estradiol valerate and dienogest are both practically insoluble in water. Both drug substances have a number of chiral centers. Dienogest does not exhibit polymorphism.

Manufacturing process

For estradiol valerate, the MAH makes use of a CEP. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia, the official handbook in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

For dienogest the ASMF-procedure is followed. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

For dienogest the manufacturing process is described in detail in the restricted part of the DMF. The structure, other characteristics and quality control of dienogest are described in the applicants's part of the DMF which is part of the Module 3, too.

Quality control of drug substance

For estradiol valerate the drug substance specification is in line with the Ph.Eur. with additional requirements for residual solvents and particle size distribution. Furthermore, the CEP specifies a more tight requirement for Ph.Eur. impurity E.

For dienogest the drug substance specification has been established in-house by the MAH. The specification is acceptable in view of the route of synthesis and the various European guidelines.

Stability of drug substance

Estradiol valerate:

Stability data on the active substance have been provided for six full-scaled batches stored at 25°C/60% RH (5 years), two full-scaled batches stored at 30°/70% RH (5 years) and two full scaled-batches stored at 40°C/75% RH (6 months). The batches were stored inside a double LDPE bag.

No changes are seen at all storage conditions for the stability indicating parameters. The claimed shelf life of 5 years is justified, without an additional storage condition.

Dienogest:

Stability data on the active substance have been provided for three full-scaled batches stored at 25°C/60% RH (5 years), 30°/65% RH (5 years) and 40°C/75% RH (6 months). The batches were stored in a transparent LDPE bag, placed inside a triple laminated bag, which is further placed inside a fibre drum. No changes or trends were observed at all storage conditions. The claimed shelf life of 5 years is justified, when stored in the original package to protect from light.

Drug Product

Composition

The film-coated tablets consist of four different formulations with active substances and one formulation do not contain active substances ('placebo' tablets). The different formulations cover a 28-day cycle of one tablet each day.

Each wallet (28 film-coated tablets) contains in the following order:

Estradiol valerate (mg)	Dienogest (mg)	Colour	Number of tablets per blister	Embossed letters
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3	-	Dark yellow	2	DD
2	2	Medium red	5	DJ
2	3	Light yellow	17	DH
1	-	Dark red	2	DN
0	0	White	2	DT

The tablets with active substances contain lactose monohydrate, maize starch, pregelatinised maize starch, povidone, magnesium stearate and a coating of hypromellose, macrogol, talc, titanium dioxide and ferric oxide red and/or yellow. The 'placebo' tablets consist of lactose monohydrate, maize starch, povidone, magnesium stearate and a coating, consisting of hypromellose, macrogol 6000, talc, titanium dioxide and ferric oxides. The tablets are packaged in PVC-Alu blisters.

The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The development is based on a standard formulation for hormone products. Holding times of the intermediates have been investigated and the dissolution method is developed.

The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process comprises a granulation, tableting and film-coating. First granulation is performed. The magnesium stearate is added to the granules and the mixture is blended. The granules are tableted by direct compression and coated by spraying an aqueous coating solution on the tablet cores.

The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full scaled batches.

Excipients

The excipients comply with the Ph.Eur. and the ferric oxides with the NF and Directive 95/45/EC. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, identity, assay, degradation, dissolution, microbial quality and uniformity of dosage units.

The release and shelf life limits are the same, except for the impurities and lower limit for assay. The different shelf life requirements are acceptable based on the increase in impurities during the stability studies. Other requirements are acceptable in view of the current regulations.

The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on five production-scaled batches of each formulation, demonstrating compliance with the release specification.

Packaging

The film-coated tablets are packaged in a PVC-Alu blister. The blister is glued into a carton wallet. The number of the day in the cycle is printed on the blister.

Stability of drug product

Stability data on the product have been provided at least three full-scaled batches of each formulation stored at 25°C/60% RH (36, 48 and 60 months), 30°C/70% RH (36, 48 and 60 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in a transparent PVC-Alu blister. For three formulations results from long-term stability studies for 60 months are available. For the fourth formulation 48 months of data are currently available.

At accelerated storage conditions only a slight increase in impurities is observed. At long-term storage conditions variability in assay of both active substances is observed. There is a minor increase in total impurities of estradiol valerate. The increase is more pronounced in tablets containing less estradiol valerate. For dienogest a minor increase in total impurities is observed.

At intermediate storage conditions, the same trends are observed as at long-term storage conditions. Furthermore a decrease in the dissolution of estradiol valerate is observed. However, this decrease is observed after 36 months. The NfG on stability testing for existing active substances and related finished products specifies the requirements for stability data for climatic zones I and II (Europe). Therefore in Europe only 12 months data at intermediate conditions are required and no additional storage conditions are necessary. Based on the stability data provided, the claimed shelf life of 60 months is justified without a special storage condition.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
 A TSE free declaration for lactose monohydrate has been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.2 Non clinical aspects

Good Laboratory Practice

Part of the non-clinical studies was carried out in accordance with Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC). Many other older studies were not in accordance with GLP and were incomplete. New studies have been conducted to replace these older ones, in accordance with GLP regulations. The MEB has been assured that sufficient non-clinical studies have been conducted in accordance with acceptable standards of GLP.

Pharmacology

Relative binding of dienogest to the progesterone receptor as compared to progesterone or other synthetic progestogens is 10 to 30 fold less. Binding to the glucocorticoid receptor and to the androgen receptor is low. Binding of dienogest to the mineralocorticoid receptor and the estrogen receptor is negligible. Other studies have showed that dienogest does not bind to the sex hormone binding globulin (SHBG) and the corticoid binding globulin (CBG).

Metabolites showed hardly any binding and activity at the steroid receptors tested with the exception of the aromatic metabolite of dienogest which has some activity for the estradiol receptor. Due to the low plasma levels at which this metabolite is present in humans, a significant estrogenic activity of this metabolite is not anticipated.

Protein binding is comparable among species, but tends to be higher in human. The strong in vivo progestational activity of dienogest in rabbits as compared to other progestagens is probably due to a higher volume of distribution and a longer residence time in rabbits as compared to other species.

Antigonadotropic activity was seen in male rats at low doses. In female rats and monkeys however, the exposures at which antiovaratory effects were seen, were higher than human exposures; at least 20 times in rats, and 2 times in monkeys.

Dienogest as compared to levonorgestrel has stronger antiprogestational properties. Dienogest as compared to Levonorgestrel has stronger estrogenic activity. Dienogest has marginal androgenic effects as compared to 3-keto-desogestrel and has clear antiandrogenic effects. Dienogest has no mineralocorticoid effects, or glucocorticoid properties.

In the safety pharmacological studies after high doses of dienogest no relevant effects on the nervous system, blood pressure, heart rate, respiratory system or on kidney functions were observed.

No pharmacodynamic drug interaction studies have been performed.

Pharmacokinetics

Overall, the pharmacokinetics/toxicokinetics of dienogest are sufficiently investigated.

Absorption

It can be concluded that dienogest was rapidly absorbed after oral administration. T_{max} in mice and rats was about 0.5 hour and in rhesus monkeys 1-2 hour (concluded from repeated dose experiments, because these are the most reliable). In rabbits, dogs and monkeys (baboon, bonnet) T_{max} varied between 2-6 hours (single dose experiments). A high absolute bioavailability (F) was observed (70% in rats, 70% in baboon, and 85% in dogs).

Distribution in normal and pregnant animals used in reproduction studies

Plasma protein binding determined by ultra-filtration was 86-99% in rats, dogs, in baboons and in humans..

The volume of distribution among species ranged from 0.6 l/kg in rats and dogs to 3.2 l/kg in rabbits.

Dienogest was rapidly distributed in female rats. At 1 hour after oral administration, the highest concentration of radioactivity in organ tissues were observed in adrenal glands, liver, stomach, ovaries and kidney. Other organs had concentrations similar or lower than blood plasma. After 21 times repeated daily oral administration of 1 mg/kg in female rats concentrations in white fat, skeletal muscle, cerebellum, blood, skin and spleen were 11-14 fold higher as compared to the data after the first administration, while in other organs 3-10 fold higher concentrations were observed.

Metabolism

In monkey and human mainly unchanged dienogest was found in plasma, while in rat plasma besides unchanged DNG some metabolites were found. It was demonstrated that the aromatic metabolite in rat plasma was responsible for the estrogenic effects seen in this species.

Only 6-8% of dienogest was excreted unchanged in urine. A number of metabolites were detected, indicating that hydroxylation plays the major role in metabolism of DNG in all species investigated. Metabolites were excreted as free steroids, glucuronoids and sulphates.

In in vitro studies with liver microsomes of rat, dog, monkey and humans approximately 30% of dienogest was metabolised. CYP3A4 was identified as the predominant isoenzyme. Dienogest does not inhibit CYP1A2, CYP2D6, CYP2E1, CYP3A4, CYP2C9 and CYP2C19.

Because of sufficient toxicity data in rat and monkey, no additional data are requested. All metabolites observed in human were also observed in these species.

Excretion

Excretion was studied in rat, rabbit, dog and monkey (baboon). Dienogest was rapidly eliminated from plasma with $t_{1/2}$ of 5-9 hrs. Radioactivity was mainly excreted via urine in all species. Biliary excretion was studied in rats and rabbits, and 30 to 50% of the radioactivity was excreted via this route. Based on the plasma concentration versus time curve in rats and mice there was evidence for enterohepatic circulation.

Pharmacokinetic drug interactions

On the basis of in vitro interaction studies, no effect on the CYP family of enzymes by dienogest is expected. At high doses, increases in liver enzymes were observed. Also at high doses, drug-drug interactions with respect to pharmacokinetics were observed between dienogest and estradiolvalerate, but clinical relevance is unlikely.

Pharmacokinetics after a single dose/repeated administration

Pharmacokinetic parameters after single dose administration were determined in mice, rats, rabbits, dogs and various strains of monkeys (bonnet, baboon, cynomolgus). In general, these single dose studies are of insufficient quality to conclude. Because of the good quality of the pharmacokinetic parameters in the toxicity studies it would not be necessary to perform additional studies with single administration.

The studies with mice and with monkeys were the only studies describing the effect of multiple dosing. In most of the multiple dose studies a linear relationship between dose and AUC was observed in the tested dose ranges.

Toxicology

Single-dose toxicity

Single-dose toxicity studies with oral administration were performed in mice, rats, rabbits and dogs and revealed a very low acute toxicity of dienogest, in particular when compared to the intended human dose. Non-lethal doses were between 1000 and 4000 mg/kg with the exception of male rabbits were it was below 1000 mg/kg. Signs of toxicity observed at high doses were central depression in mice, none in rats, anorexia, weight loss and convulsions in rabbits and a transient increase in GPT in dogs without histopathological findings.

Repeated dose toxicity

A large number of oral repeated dose toxicity studies with dienogest was provided in rats (4 studies: one 1 year study in females, two 6 month studies in both sexes, with dose in the range of 0.1 - 10 mg/kg/day, one 3 month study in females, dose range 0.3-30 mg/kg/day), Rhesus monkeys (an one year and a 3 months study both with dose range of 0.1-10 mg/kg/day), dogs (1 month, 3 months and 6 months, dose ranges of respectively 0.1-10 mg/kg/day, 0.03-3 mg/kg/day and 0.01-1 mg/kg/day) and mice (3 months, 5-125 mg/kg/day). A sufficient number of studies (e.g. one year rat, one year monkey) was carried out according to GLP guidelines.

In all four species predominantly the expected pharmacological effects on the reproductive system were found. Furthermore, effects were found on liver and on serum parameters (cholesterol, blood clotting factors, alkaline phosphatase) and red blood parameters.

In rats effects consisted of, e.g. decrease of estrous cycle, effects on uterus (decreased weight, thinning of wall, decrease of uterine glands), vagina (epithelial mucification), ovary (e.g. increased relative organ weight, decrease of Graafs follicles, increase of corpora lutea), mammary glands (increase in weight, size or activity, both sexes), pituitary (increase of chromophobe cells, both sexes), testes (atrophy) and spermiogenesis (decreased). In addition signs of effects on the liver were observed (fat deposition in some studies, decreased phospholipid content), no effects on liver function as examined by means of bromsulfalein were found. Some effects on serum cholesterol (decrease) and free fatty acids (increase in one year study) and blood clotting factors indicated effects on liver metabolism. Only in the three months study a decrease of red blood cell parameters was observed. Most effects were reversible, but some effects on the female reproductive organs persisted for one month after termination of treatment.

In monkeys effects consisted of discontinuation of menstruation. The following changes were found on reproductive organs: hyperplasia of the interstitial cells of the uterine intima and thinning of the basal layer, vaginal epithelial atrophy and follicular atresia. The follicular atresia reflected continuing inhibition of ovulation during the one year study. The uterine intima was necrotic (focal hemorrhagic) and the relative uterus weight was increased after high dose administration. Increased serum phospholipids indicated that the drug affected lipid metabolism. Only in the middle dose group effects on blood clotting factors were found, but the blood coagulation and fibrinolysis capacity were not affected. Alkaline phosphatase activity in bone, liver and serum was inhibited in a dose-related manner.

Female dogs showed the following effects: inhibition of heat, decrease of absolute ovary weights and increase of relative uterus weight. Mammary glands as well as the pituitary cells (prolactin-forming) were hyperplastic. The study revealed also muco- and pyometra. Moderate atrophy of the zona reticularis in the adrenals was found. Serum proteins, triglycerides and β -lipoprotein were also increased. Two months after termination of treatment, effects on the reproductive system had not yet completely disappeared.

In mice, periacinar hepatocytic hypertrophy was observed at the highest dose. In addition, only the expected pharmacological effects on the endocrine system were found.

It is noted that effects on ECG were not examined in any of the studies.

The toxicity profile of the combination therapy is very similar to those of the individual components, and is thus not likely to result in any safety concerns.

Reproduction studies

Reproductive toxicity was studied in rats, mice, and rabbits. These studies comprised fertility/early embryonic development to implantation and embryo-fetal development in mentioned animals. There were no remarkable effects except embryotoxicity only at maternally toxic doses.

Mutagenic potential

A full battery of negative *in vitro* mutagenicity tests was obtained with dienogest; the Ames test, the TK locus mutation test, UDS assay and the chromosomal aberration test. *In vivo* the mutagenicity of Dienogest was found to be negative in the UDS assay in rats, the micronucleus test in mice and a liver foci bioassay in rats. On basis of the presented studies, it can be concluded that dienogest has no mutagenic potential.

Oncogenic/carcinogenic potential

Three carcinogenicity studies with dienogest were conducted, one in the mouse and two in the rat. In general, dienogest produced effects which could be expected based on its hormonal action.

In male mice (B401) a non-significant increase of hemopoietic malignant lymphomas and pituitary adenomas was observed. In female mice an increased incidence of benign stromal polyps in the uterus

was observed at doses of 100 mg/kg body weight/day, which is a factor 12 times higher compared to the human therapeutic level based on AUC values.

In the first rat study (B399), in male rats no increase of tumours was observed. In female rats a slight increase of mammary hyperplasia and mammary gland adenomas was observed after exposure to dienogest at levels of approximately 0.12 and 1.24 mg dienogest/kg body weight, which corresponds to a fraction of the human therapeutic dose level based on AUC values. Norgestrel, used as a positive control, did not show any effect on the mammary area. Critical comments on this study were that the highest dose did not exceed the human intake based on AUC levels.

In the second rat study (B398) observed neoplastic changes in male rats were an increase of benign pituitary adenomas, benign adenomas in the kidney and benign fibroepithelial tumours in the mammary area. These changes were observed at 10 mg/kg bw, which is a factor 7 above the human intake based AUC levels. In female rats small non-neoplastic effects on the mammary area and the endometrium were observed but no increase of tumours was found. Critical comment on this study was that the mortality throughout the experiment was high; less than 20% of the male animals survived till the end of the trial.

It is concluded that no unexpected effects of dienogest were observed. The observed tumour types were indicative for the (weak) estrogenic properties of dienogest.

No combination studies with estrogen valerate and dienogest were performed. It was argued that it was not useful to test the combination of estrogen valerate and dienogest because the ratio of these compounds in human does not reflect the physiological condition of the test species and it was shown that dienogest has a strong progestogenic capacity which will inhibit estrogen induced tumour formation. Therefore additional carcinogenicity studies with the combination of estradiol valerate and dienogest are not necessary.

It is concluded that dienogest has no carcinogenic potential in rodents which is relevant to human health.

Special toxicity studies

Dienogest caused no antigenicity in tests for Active Systemic Anaphylactic (ASA) reactions in guinea pigs, and heterogeneous Passive Cutaneous Anaphylaxis (PCA) reactions in rats to sensitized mouse serum. Evidence for immunomodulation was suggested in a published report. In functional assays in mice, dienogest affected neither the graft versus host reactions nor the rejection reaction of skin allografts, but it dose-dependently stimulated humoral antibody formation against sheep erythrocytes. The results from other repeated dose studies gave no indications for immunomodulating effects. No effects of progestins on SRBC assay with mice were reported. The stimulation of humoral antibody formation might be the estrogenic activity of dienogest. Therefore, no immunotoxic potential of dienogest is to be expected.

Ecotoxicity/Environmental risk assessment

Based on the provided information for Qlaira, a risk posed by the drug substance estradiol(-valerate) for surface water is determined. For groundwater and sediment the risk is acceptable; for sewage treatment and soil the risk assessment could not be completed.

Based on the provided information for Qlaira, a risk posed by the drug substance dienogest for surface water is determined. For soil, sewage treatment and groundwater risk is acceptable; for sediment the risk assessment could not be completed.

For both substances post-approval commitments were agreed to complete the environmental risk assessment.

II.3 Clinical aspects

Quality of clinical studies, compliance with GCP

The MAH declares that all clinical studies performed in the framework of this submission were conducted in accordance with Good Clinical Practice, the principles of the Declaration of Helsinki, and all applicable national regulations valid at the time the studies were performed, and that the protocols and protocol amendments were reviewed and approved by Independent Ethics Committees or Institutional Review Boards.

Pharmacokinetics

Absorption

After oral administration of DNG either as immediate-release tablets or as a microcrystalline suspension, the absorption of the drug was rapid as indicated by the short time of 0.67 to 2 h to reach maximum concentrations of DNG in serum. Maximum serum concentrations at steady state are reached at about 1 hour after the oral administration of Qlaira containing 2 mg EV/3 mg DNG. The absolute bioavailability of 2 mg DNG was estimated to be 91% indicating almost complete absorption and a small firstpass effect.

Dose linearity of DNG pharmacokinetics was observed following single dose oral administration of DNG tablets over a dose range of 1 to 8 mg to young Caucasian. Linear pharmacokinetic behavior of DNG was also observed when administered as a single dose in combination with 4 mg EV and in combination with 2 mg EV in postmenopausal women.

Food decreased the rate of absorption of dienogest by nearly 30% but not the extent. Since DNG is a highly soluble and highly permeable drug, the observed food effect is likely caused by the delay in gastric emptying time.

Similarly, food did not affect the extent of absorption for E2 but increased the rate of absorption as C_{max} was increased by 23% under fed conditions. Such an increase appeared to be the result of increased solubility of estradiol with high-fat meals. The biotransformation of E2 to E1 was not affected by the concomitant food intake.

Therefore Qlaira tablets can be taken without regard to meals during all phases of the Qlaira regimen which is supported by the fact that all of the clinical trials with the Qlaira tablets were performed without any restrictions concerning food.

Distribution

After oral administration of Qlaira, post-maximum concentrations declined biphasically with a terminal half-life of about 12 hours. A fraction of 10% of circulating DNG is present in the free form with approximately 90% being bound non-specifically to albumin. DNG does not bind to the specific transporter proteins SHBG and CBG. Thus, DNG pharmacokinetics are not influenced by changes of SHBG or CBG concentrations and displacement of testosterone from SHBG or cortisol from CBG by DNG is unlikely.

The volume of distribution at steady state ($V_{d,ss}$) of DNG is 46 l after the intravenous administration of 85 μg ^3H -dienogest.

Metabolism and Elimination

DNG is nearly completely metabolized by the known pathways of steroid metabolism (hydroxylation, conjugation), with the formation of mostly inactive metabolites. Within the first 24 h after administration, 59% of circulating radioactivity is attributable to unchanged DNG, there was no major peak besides unchanged DNG; the proportion of water-soluble conjugates or metabolites is relatively low. Nevertheless, the in vivo biotransformation of DNG is very intensive, only approximately 6 to 8% DNG is excreted unchanged, mainly in conjugated form. Its metabolites are excreted as free steroids, glucuronides, and sulfates in all species investigated.

In vitro CYP3A4 was identified as a predominant enzyme catalyzing the metabolism of DNG, whereas CYP1A2, CYP2C9, CYP2A6, CYP2C19, CYP2D6 and CYP2E1 are not involved in vitro.

At a multiple of the clinically relevant concentration, DNG does not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E, and CYP3A4. The inhibition constant K_i , calculated for CYP2C19 and CYP3A4, was more than 100-fold the maximum serum concentration observed after oral administration of the 2 mg EV/3 mg DNG tablet contained in Qlaira. Therefore, it is to be concluded that DNG at clinically relevant doses will not affect the metabolism of other drugs metabolized by cytochrome P450 enzymes.

DNG and its metabolites are predominantly excreted with the urine. In total, 42% of the applied dose was renally eliminated within 24 h, 63% within 6 days, and the total elimination by urine and feces amounted to 86% after 6 days. In urine, approximately 20% of the steroids are unconjugated. The remainder consists of conjugates and other polar substances, with approximately equal proportions of glucuronides and sulfates.

Pharmacokinetics at steady-state

Steady state is reached after daily administration for 3 days of the 2 mg EV/3 mg DNG dose. Trough, maximum and average DNG serum concentrations at steady state are 11.8 ng/ml, 82.9 ng/ml and 33.7 ng/ml, respectively. The mean accumulation ratio for AUC (0-24h) was determined to be 1.24. The pharmacokinetic parameters of DNG at steady state following 2 mg EV/3 mg DNG in fertile women are similar to those observed in postmenopausal women with the same dose.

The pharmacokinetics of DNG are comparable over multiple treatment cycles in healthy, fertile women, indicating that the pharmacokinetics of DNG are cycle-independent and do not change during long-term therapy.

Pharmacokinetic Drug-drug Interactions

As DNG and E2 are substrates for CYP3A4 and an effect of known CYP3A4 inhibitors and inducers on DNG and E2 metabolism is possible, two drug-drug interaction studies were performed with the Qlaira tablets. Coadministration of rifampicin with Qlaira tablets showed a significant decreases in steady state concentrations and systemic exposures of DNG. The systemic exposure of DNG at steady state, measured by AUC(0-24h), was decreased by 83%. Similarly, significant decreases in steady state concentrations and systemic exposures of E2 were observed. The systemic exposure of E2 at steady state was decreased by 44%.

Known CYP3A4 inhibitors like azole antifungals, cimetidine, verapamil, macrolides, diltiazem, antidepressants and grapefruit juice may increase plasma levels of DNG and E2. Co-administration with the strong inhibitor ketoconazole resulted in a 186% increase of AUC(0-24h) at steady state for DNG and a 57% increase of AUC(0-24h) for E2. When co-administered with the moderate inhibitor erythromycin, the AUC (0-24h) of DNG and E2 at steady state were increased by 62% and 33%, respectively .

Combined administration of DNG together with EV has no effect on DNG pharmacokinetics. The same holds true for EV, whereby combined administration of EV together with DNG has no effect on EV pharmacokinetics.

Special populations

No studies in patients with impaired renal function were performed. However, according to the MAH no special risk for these patients is to be expected, since DNG is metabolized before excretion and its metabolites are pharmacologically inactive.

No studies were performed in patients with impaired liver function because severe liver diseases are contraindicated.

No studies were performed in children because Qlaira is not indicated before menarche.

No population pharmacokinetic analysis was carried out by the MAH.

Pharmacodynamics

Effects of DNG

Despite its low affinity to the progesterone receptor, DNG was shown to have strong peripheral progestogenic effect on the endometrium. . Two studies characterized the progestogenic activity of DNG by the determination of the transformation dose in estrogen-deficient women who were treated with EE for 2 weeks and with a combination of EE and DNG for 2 consecutive weeks. However, a complete transformation of the endometrium in 100% of the volunteers could not be documented at any of the doses tested up to 0.55 mg DNG.

Daily administration of 0.2 or 0.4 mg DNG for 21 days showed a progestogenic effect on the cervical secretion in normocyclic women. In estrogen-deficient women treated with 0.05 mg EE, the additional administration of 0.1 to 0.55 mg DNG had an anti-estrogenic effect on the cervical secretion. The anti-estrogenic effect was independent of the dose of DNG, suggesting that the maximum effect was already reached at a dose of 0.1 mg. DNG has a slight anti-estrogenic effect on the proliferation of the vaginal epithelium during the pre-ovulatory phase of normocyclic women

The ovulation inhibition dose of DNG was determined in healthy young women. Basis for judgment was the concentration of progesterone in serum supported by measurements of E2, FSH, and LH. Doses equal to or greater than 1 mg DNG per day inhibited ovulation. However, follicular maturation processes evident by a rise in serum E2 levels were not completely suppressed even with the highest dose of 2 mg DNG.

Effects of EV compared to EE

The MAH investigated whether substitution of EE with EV in Qlaira offers additional benefit due to the supposed lower estrogenicity of EV. The MAH concluded, also from literature, that 20 µg EE compared to

2 mg EV is comparable to or greater at the antigonadotropic level, slightly more active at the endometrial level, comparable at the vaginal level, more active at the hepatic level. The lower activity on the hepatic level has however not been clinically shown with the dose regimen for the current application.

Inhibition of ovulation with Qlaira

In view of the current application, **inhibition of ovulation** is the major pharmacodynamic action of interest. After inadequate ovulation inhibition in earlier studies with lower dose regimens (1-2 mg DNG), a ovulation inhibition study was conducted for this application investigating higher doses, Qlaira (2-3 mg) versus the 'DNG-increased regimen' (3-4 mg). The Hoogland score was found to be only slightly better for the 'DNG increased regimen' (only 2 women with ovulation in cycles 2 and 3) than for the Qlaira tablets with 5 ovulating volunteers in cycle 2 and 3. However, both regimens were comparable with regard to other measurements indicating suppression of ovarian function. The Qlaira (2-3 mg) regimen was therefore selected for further development.

Contraceptive efficacy

Two phase III studies were conducted, of which the large long-term study (A35179) is considered pivotal. The second comparative study primarily focussed on **bleeding control** (A35644) (see also table 1). Furthermore, an US study has been conducted and submitted later in the procedure (A39818).

Table1: Overview of European and US clinical phase III studies and design of the studies.

Study (protocol no.)	Study design	Total no. of women by treatment group*	Treatment duration	Efficacy parameters
A35179	Multicenter, open, uncontrolled, one-arm	Qlaira: 1377 (18 to 50 years) By age subgroups: 998 (18 to 35 years) 379 (36 to 50 years)	20 cycles	Primary: number of pregnancies (unintended pregnancies during study treatment) Secondary: bleeding patterns and cycle control The subjective assessment of treatment by women was also evaluated
A35644	Multicenter, double-blind, double-dummy, controlled, randomized	Qlaira: 399 (18 to 50 years) By age subgroups: 199 (18 to 35 years) 200 (36 to 50 years) Miranova**: 399 (18 to 50 years) By age subgroups: 201 (18 to 35 years) 198 (36 to 50 years)	7 cycles	No distinction was made between primary and secondary variables The following efficacy variables were investigated: - bleeding patterns - cycle control - cycle control for cycles 2 to 7 - number of unintended pregnancies - subjective assessment of treatment by the women - mean change in the PGWBI total score and subscale scores from baseline to treatment cycles 4 to 7 - change in the MFSQ subscale scores from baseline to treatment cycles 4 and 7
A39818	Multicenter, open, uncontrolled, one-arm	Qlaira: 490 (18 to 35 years)	13 cycles	Primary: number of pregnancies (unintended pregnancies during study treatment) Secondary: bleeding patterns and cycle control

*Note: the number of women refers to the full analysis set

**Microgynon or Miranova are identical names for the same products, 1-21 days 0.03 mg EE + 0.15 mg LNG

MFSQ = Mc Coy Female Sexuality Questionnaire

PGWBI = Psychological General Well-Being Index

The study participants started tablet intake on the first day of withdrawal bleeding at the beginning of the first medication cycle and recorded compliance and bleeding patterns through a diary.

Table 2: Study treatment during each 28-day cycle and handling missed pills

Days	Content of EV/DNG	Actions (if delay > 12 hours)
1 to 2	3.0 mg EV	1. Intake of missed tablet immediately and the following tablet as usual and 2. Use of backup contraception until Day 9
3 to 7	2.0 mg EV + 2.0 mg DNG	1. Intake of missed tablet immediately and the following tablet as usual and 2. Use of backup contraception for the next 7 days
8 to 17	2.0 mg EV + 3.0 mg DNG	
18 to 24	2.0 mg EV + 3.0 mg DNG	1. Intake of missed tablet and continuation of tablet intake as usual (intake of all tablets from the blister in the given sequence) and 2. Use of backup contraception until Day 9 of the following cycle
25 to 26	1.0 mg EV	1. Intake of missed tablet (no further action)
27 to 28	Placebo	

Missed pills were handled according table 2, which is different from the advice given in the SPC.

- **General inclusion/exclusion criteria**

Healthy women between 18 and 50 years, smokers maximum age of 30 at inclusion, Papanicolaou (Pap) smear taken or non-suspicious Pap smear within the last six months prior to start, and at least three cycles had to follow delivery, abortion, or lactation before start of treatment, were included.

Exclusion was mainly focussed on pregnancy, lactation, presence of liver disease, vascular disease, uncontrolled thyroid disorder, uncontrolled hypertension, diabetes mellitus, tumors (known or suspected), other severe diseases that might interfere, substantial overweight, prohibited concomitant medication.

The most important **baseline characteristics** are in line with the inclusion and exclusion criteria in both studies. Almost only Caucasians were included in both studies.

- **Statistical methods**

Contraception

- The unadjusted Pearl Index and the corresponding 95% CI were to be calculated according to the EMEA Note for Guidance on Clinical Investigation on Steroid Contraceptives in Women (EMEA. CPMP/EWP/519/98.) as planned in the Study Protocol. Cycles with back-up contraception were excluded.
- The adjusted Pearl Index for method failure and the corresponding upper confidence limit were calculated with the same methods as were used for the unadjusted Pearl Index. For the calculation of time of correct treatment exposure, treatment cycles that were not considered compliant and cycles with back-up contraception were excluded.
- Additionally, a life-table analysis (survival analysis) was performed. The cumulative failure rate, i.e., the probability of getting pregnant, was calculated using the Kaplan Meier estimator on the basis of the known pregnancies under treatment (Kaplan EL and Meier P, 1958).

The **bleeding pattern** indices were analyzed using the following descriptive statistics: Number of non-missing observations, arithmetic mean, SD, minimum, 1st quartile, median, 3rd quartile, and maximum. The statistics were calculated for each reference period. Additionally, 95% confidence intervals were calculated for bleeding/ spotting days *per* reference period, age group, and treatment group.

- **Results on contraceptive reliability**

The number of pregnancies observed in the pivotal clinical trials are given in table 3.

Table 3: Unadjusted Pearl Index (PI_U) and Adjusted Pearl Index (PI_A)

A39818, A35179, and A35644, Treatment: EV/DNG tablets						
Age group	Total time of exposure [days]	Days with back-up contraception	Relevant exposure time [days]	Number of pregnancies	PI _U	Upper limit of two-sided 95% CI
18-35	684030	30763	653267	18	1.0064	1.5906
18-50	914918	33968	880950	19	0.7878	1.2302

A39818, A35179, and A35644; Treatment: EV/DNG tablets							
Age group	Total time of exposure [days]	Days with back-up contraception	Days non-compliant	Relevant exposure time [days]	Number of pregnancies	PI _A	Upper limit of two-sided 95%- CI
18-35	684030	30763	8939	644328	9	0.5102	0.9685
18-50	914918	33968	9859	871091	10	0.4193	0.7711

The **unadjusted Pearl Index (PI_U)** based on pooled data across studies A35179 and A35644 conducted in the EU for women aged 18-50 years is **0.65** (upper limit 95% CI 1.11), and **0.87** (upper limit 95% CI: 1.52) for women aged 18-35 years, obtained with adequate precision as requested in the CHMP guideline, i.e. the upper limit of the 95% CI is within one from the point estimate.

The **Pearl index for method failure (PI_A)** is **0.30** for women aged 18-50 and **0.37** for women aged 18-35 years, and therefore comparable with that noted for other combined oral contraceptives.

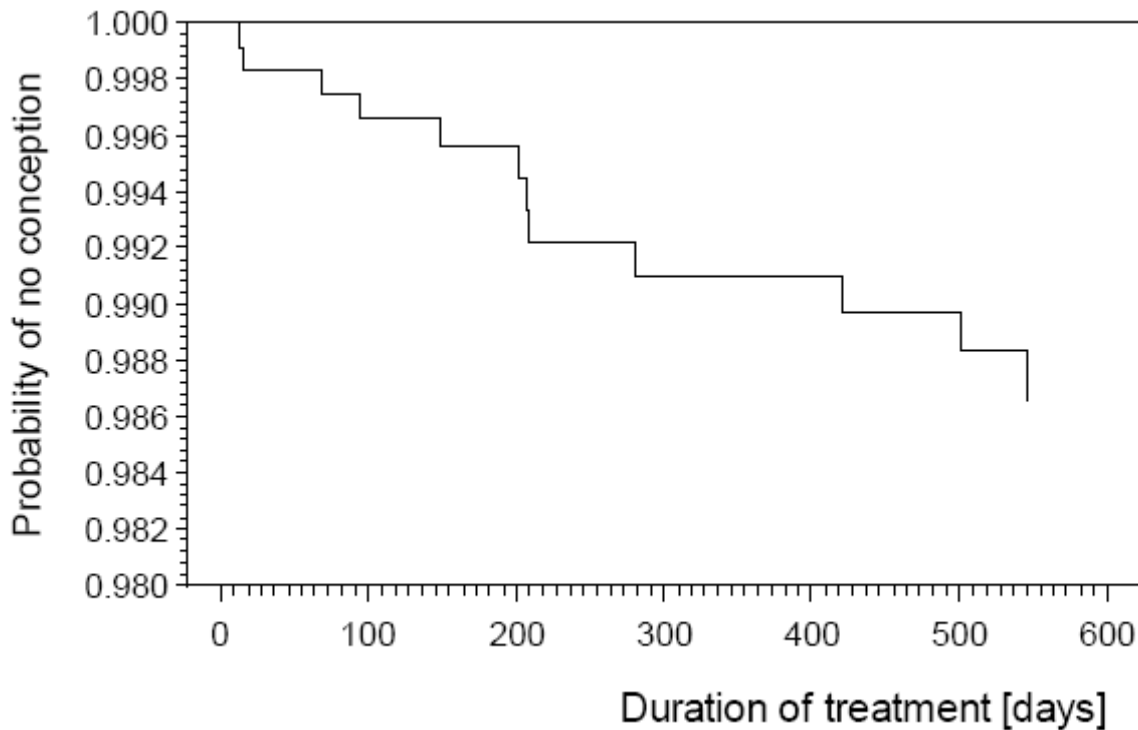
The relative contraceptive efficacy compared to other combined oral contraceptives (based on the Pearl Index for method failure) cannot directly assessed as there is no comparative trial assessing contraceptive reliability. Indirect comparison suggests a lower contraceptive efficacy in comparison to approved standard dosed second and third generation contraceptives e.g. Yasmin. However, it should be taken into consideration that the age groups are different, i.e. respectively 18-35 years of age and 18-50 years. Up to now only overall analyses were calculated based on the age group of 18 to 40 or 45 years.

Taken the **US study A39818** separately, the **unadjusted Pearl Index (PI_U)** for women aged 18-35 years is **1.45** (upper limit 95% CI 3.16) and **1.00** for **method failure (PI_A)** (upper limit 95% CI 2.57). Combined with the European studies the **unadjusted Pearl Index (PI_U)** for women aged 18-35 years is **1.01** (upper limit 95% CI 1.59) and **0.51** for **method failure (PI_A)** (upper limit 95% CI 0.97). For women aged 18-50 years the unadjusted (PI_U) is 0.79 (upper limit 95% CI 1.23) and 0.42 for method failure (PI_A) (upper limit 95% CI 0.77) as given in table 5.

The study size requirements and pregnancy reporting of the NtG on clinical investigation of steroid contraceptives in women regarding efficacy for a new contraceptive method are considered fulfilled:

- The calculation of efficacy was based on the Pearl Index and life table analysis.
- The difference between the point estimate and the upper limit of the 95% confidence interval does not exceed 1.
- At least 400 women have completed one year of treatment
- No relevant differences in demography between the women in the Qlaira and Miranova/Microgynon® groups, respectively.

Figure 1: Survival curve for Kaplan Meier estimate – study A35179 (FAS, women aged 18 to 50 years)



- **Results on cycle control**

A **withdrawal bleeding** episode during treatment was **defined as** the first bleeding episode after the last day of progestogen intake (i.e. after day 24 for Qlaira or after day 21 for Miranova). In case a bleeding episode was ongoing on the last day of Qlaira or Miranova intake and on the following day, this episode was regarded as the withdrawal bleeding episode, provided it started not more than 4 days before withdrawal of Qlaira or Miranova. All other (unexpected) bleeding episodes were considered as **intracyclic bleeding**. If no bleeding occurred until the next withdrawal of the progestogen component, this was assessed as absence of withdrawal bleeding in the previous treatment cycle (provided that pregnancy had been excluded).

Qlaira shows less withdrawal bleedings than the comparator and in general of less intensity than with the comparator Miranova. There were generally more intracyclic bleedings and they tend to be more severe with Qlaira (see table 4). However, the total number of days with bleeding/spotting is less with Qlaira. Based on patient diaries from a comparative clinical trial, the percentage of women per cycle experiencing intracyclic bleeding was 10 – 18 % for women using Qlaira. Amenorrhea occurs in approximately 15% of cycles. Overall, there are not many differences between groups.

Table 4: Numbers and % of volunteers with intracyclic bleeding - PPS

	Age 18 – 50 years		Stratum 18 – 35 years		Stratum 36 – 50 years	
	Treatment	Comparator	Treatment	Comparator	Treatment	Comparator
Cycle 1	68 (18.9)	61 (17.1)	32 (18.5)	30 (16.9)	36 (19.3)	31 (17.2)
Cycle 2	57 (15.8)	43 (12.0)	35 (20.2)	17 (9.6)	22 (11.8)	26 (14.4)
Cycle 3	41 (11.4)	49 (13.7)	22 (12.7)	27 (15.3)	19 (10.2)	22 (12.2)
Cycle 4	55 (15.3)	38 (10.6)	35 (20.2)	17 (9.6)	20 (10.7)	21 (11.7)
Cycle 5	39 (10.8)	37 (10.4)	17 (9.8)	19 (10.7)	22 (11.8)	18 (10.0)
Cycle 6	37 (10.3)	35 (9.8)	23 (13.3)	18 (10.2)	14 (7.5)	17 (9.4)
Cycle 7	46 (12.8)	35 (9.8)	24 (13.9)	16 (9.0)	22 (11.8)	19 (10.6)

In the **US study A39818**, the number of bleeding and spotting days, the length of bleeding or spotting episodes, number of subjects with withdrawal bleeding, were similar as seen with the other 2 pivotal EU studies. The number of intracyclic bleeding tended to be slightly more.

Ongoing studies

Two clinical phase 3 studies are ongoing to investigate Qlaira for the treatment of dysfunctional uterine bleeding (DUB). These studies are not considered relevant to this submission for the indication of oral contraception.

Clinical safety

- **General AE's and discontinuation**

Out of 1776 Qlaira -treated women (pooled data across studies A35179 and A35644 conducted in the EU), a total of 187 **Adverse Events (Aes) leading to premature discontinuation** were recorded for 155 (8.7%). The most frequently reported AEs leading to study discontinuation included metrorrhagia (24 women, 1.4%), acne (15 women, 0.8%), weight increase (13 women, 0.7%), headache (9 women, 0.5%), depression (8 women, 0.5%), hypertension (8 women, 0.5%), cervical dysplasia (6 women, 0.3%), decreased libido (6 women, 0.3%), and breast pain (5 women, 0.3%). Other AEs leading to discontinuation were reported for fewer than 5 women each. In the Miranova group, 20 AEs leading to discontinuation of the study medication were reported for 13 (3.3%) women. The most frequently reported AEs leading to discontinuation were acne (4 women), weight increase (3 women) and migraine (3 women). Other AEs leading to withdrawal were reported for 2 or 1 woman only.

A direct comparison of Qlaira and Miranova in study A35644 revealed that common **drug-related AEs** under Qlaira were breast pain (3.3%), headache (1.8%), and acne (1.3%) and differed in ranking and type from those documented under Miranova (acne [2.3%], headache [1.8%], migraine [1.3%], alopecia [1.0%], breast pain [1.0%]; and weight increase [1.0%]). No age-related differences were observed with regard to the frequency of drug-related AEs.

- **Serious adverse events**

Serious adverse events do not show a safety pattern deviating from that known for other COCs. A total of 65 SAEs were recorded for 48 (2.7%) out of 1776 Qlaira -treated women, of which 5 were classified as drug-related (against 3 drug-related in the Miranova-group).

Gynaecologic examination included breast palpation, TVU (Transvaginal ultrasonography), cervical smear for all subjects, with 18 (1.1%) in the Qlaira group and 3 (0.8%) in the Miranova group found PAP III or worse. Endometrial biopsies for 219 women in study A35179 revealed **endometrial metaplasia** in 2 women (0.9%) specified as "limited". Serious adverse events do not show safety pattern deviating from that known for other COCs. Three women were reported with cervical carcinoma stage 0, which had no impact during follow-up.

Two **deaths** were reported which were not considered related to the study treatment (one in natural disaster, one due to aneurysm).

No venous thromboembolisms (VTE's) were reported.

Except for one case of myocardial infarction in a woman at high risk, no further **arterial thromboembolic events** were reported.

Specific safety studies

An overview of specific safety studies is given in tabel 5

Table 5 Further studies relevant for laboratory evaluations including metabolism and hemostatis parameters

Study (protocol no) Phase	Main study objective	Design	Total no. of women by treatment (FAS)	Treatment duration
A33022 (301886) Phase 2	Plasma lipids, hemostatic variables and carbohydrate metabolism	Single-center, open-label, controlled, randomized	EV/DNG 30 Triquilar 28	7 cycles
A38220 (310122) Phase 2	Hemostatic parameters	Single-center, open-label, crossover controlled, randomized	EV/DNG 27 * Microgynon 29*	3 cycles per period
A25364 (307300) Phase 2	Ovulation inhibition	Multicenter, open-label, randomized, comparative	EV/DNG 100 'DNG-increased regimen' 103	3 cycles

• **Laboratory findings**

For **liver enzyme** investigation in the A35644 study, 1 subject (0.3%) in Qlaira and 3 (0.8%) in Miranova had a clinical relevant change of GGT and ALAT 1 subject (0.3%) and 1 (0.3%) had a clinical relevant change in ALAT, and no clinical relevant changes appeared in AP and cholinesterase.

Glucose mean HbA1c levels remained normal for both groups in study A35644.

For the comparative study A35644 versus Miranova, no differences in **lipid metabolism** between treatment groups were observed.

In the cross-over study A38220, following 3 treatment cycles, **mean SHBG** concentrations increased to comparable levels from 48.80 ± 19.335 to 72.61 ± 27.952 nmol/L for Qlaira and from 51.73 ± 21.269 to 72.60 ± 30.123 nmol/L for Miranova.

• **Effects on haemostatic variables/VTE risk**

The haemostatic cross-over study with Miranova (A38220) is considered of more value than the comparative study versus a tri-phasic LNG-containing COC. Tri-phasic LNG COCs are reported to have higher VTE risk than mono-phasic LNG-containing COCs. In study 38220, although there is a suggestion of less effect on variables selected in the EV/DNG group, the differences are very small, i.e. the results on haemostatic parameters were rather comparable for Qlaira compared to Miranova.

The MAH committed that after the launch of Qlaira, a large comparative **post-marketing safety** surveillance study will be conducted to assess the **VTE risk** of Qlaira compared to other COCs in a non-selected target population. The comparator is a second generation COC e.g. Miranova/Microgynon.

• **Safety of US study A39818**

The safety profile was considered similar to the safety profile found in the European phase III studies. Most frequently reported **drug-related AEs** were metrorrhagia (12.4% of women), headache (7.5% of women), and amenorrhea (7.3% of women). A total of 73 (14.9%) women **discontinued** study medication **as a result of an AE**. One woman had an **abnormal cervix biopsy and an adenocarcinoma of the cervix** and recovered after surgery. For 13 women **cervical dysplasia** (i.e. PAP smears with outcome ASCUS, low grade SIL or CIN1) was reported. No AEs relevant to the risk of VTE were reported in the course of this study.

The **drug-related AEs** from the two European studies A35179 and A35644 pooled with the US study A39818 (N=2,266 women) are presented in the SPC.

Pharmacovigilance System and Risk Management System

Pharmacovigilance System

The RMS considers that the Pharmacovigilance system as described by the MAH fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management System

- The MAH committed that after the launch of Qlaira, a large comparative **post-marketing safety** surveillance study will be conducted to assess the **VTE risk** of Qlaira compared to other COCs in a non-selected target population.

- The MAH committed that soon after the launch of Qlaira a preferential prescribing monitoring program (observational study) will be conducted.

Further the MAH committed to perform additional safety studies as mentioned under commitments below.

Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The user test was performed in 2 test phases with 10 subjects each. The test persons were women of childbearing potential age (15 to 50 years), 50% of whom are or have been users of oral contraceptives. Inclusion and exclusion criteria were specified in the protocol. Test persons were able to read and speak English. Educational levels correspond with the inclusion criteria set in the protocol.

The test was performed by face-to-face interviews. Questions were designed to determine whether users can identify key information that is necessary for appropriate use. There were sufficient questions about the critical sections and the areas traceability, comprehensibility and applicability were sufficiently covered. The test included 14 questions related to the content of the package leaflet. Eight questions were related to critical safety information, 2 questions addressed the readability of the presentation of side effects, and 4 questions were focused on the correct use. Another three questions were related to the structure/appearance of the PL, The results of the test were satisfactory. In round 1 at least 9 of 10 participants were able to locate the requested information and give the correct answer for all 14 questions. All participants appeared to make use of the table of contents. No changes to the booklet were therefore warranted after the first test round. In the second round, information was found for 13 of 14 questions and explained correctly by at least 9 of the participants. The investigators gave recommendations for improvement only with regard to some minor grammatical and typographical errors, as well as medical translation to lay terms.

III BENEFIT RISK ASSESSMENT

The applicant proposes an indication for 'oral contraception' for the combination of estradiol valerate (EV) combined with dienogest (DNG). The applicant proposed additionally claims that due to the estradiol valerate component instead of the standard used ethinylestradiol, Qlaira leads to lower hepatic effects when compared to a triphasic EE/LNG-containing COC. Further, the applicant proposed claims that the impact on SHBG levels and hemostasis parameters was shown to be lower.

- **Benefit**

With an uncontrolled open phase III study, a controlled comparative phase 3 study, and a US open-label uncontrolled study, contraceptive efficacy has been sufficiently shown as the overall (ITT) Pearl Index of Qlaira

the combined is within the upper range of Pearl indices noted with approved combined oral contraceptives, while the Pearl index for method failure is comparable with that noted for other combined oral contraceptives. Furthermore, these figures were obtained with adequate precision as requested in the CHMP guideline (EMA/CPMP/EWP/519/98 Rev 1.), i.e. the upper limit of the 95% CI is within 1.0 from the point estimate. The open phase 3 studies, including sufficient number of women, had a new design by including women of 18-50 years of age and a protocol stratification of young aged women (18-35 years) and older age women (36-50 years), while up to now only overall analyses were calculated based on the age group of 18 to 40 or 45 years. This should be taken into consideration when comparing to standard dosed second and third generation contraceptives e.g. Miranova. This can however not be assessed as there is no comparative trial assessing contraceptive reliability. Indirect comparison suggests a slightly lower contraceptive efficacy for Qlaira.

In the controlled comparative study, Qlaira shows less withdrawal bleedings than the comparator and in general of less intensity than with the comparator Miranova. Based on patient diaries from a comparative clinical trial, the percentage of women per cycle experiencing intracyclic bleeding was 10 – 18 % for women using Qlaira. Amenorrhea occurs in approximately 15% of cycles.

- **Risk**

Clinical safety of Qlaira was adequately documented. Both European phase III studies included a sufficient number of women with sufficient duration of exposure according to the Guideline on clinical investigation of steroid contraceptives in women . No unexpected adverse events appeared with the use of Qlaira. The adverse events reported are known to be associated with the use of oestrogens and progestagens. The pattern of adverse drug reactions (ADRs) observed during treatment with Qlaira is considered typical for a combined oral contraceptive and did not deviate from that observed in the references group treated with Miranova. Also the phase III US study did not deviate from this safety profile.

Evaluation of endometrial effects, in general, showed a pattern known for COCs. The 2 cases of endometrial metaplasia and the 3 cases of cervical cancer (1 invasive, 2 stage 0) had no impact during follow-up.

Serious adverse events do not show safety pattern deviating from that known for other COCs.

Regarding effects on haemostasis, a comparative cross-over phase II study on haemostatic parameters is included, with a comparator with an established VTE risk profile, according to the recommendations in CHMP guideline, showing hardly any differences in effects.

However, registration dossiers are too limited to adequately quantify the risk of rare events such as VTE. Therefore, the MAH committed that after the launch of Qlaira, a large comparative post-marketing safety surveillance study will be conducted to assess the VTE risk of Qlaira compared to other COCs in a non-selected target population. The combined cohort will include 50,000 women recruited in the United States and Europe. Patients should undergo follow-up for at least 3 years.

The MAH has proposed additional claims in pharmacodynamic properties concerning hepatic effects, and lower impact on SHBG levels and hemostasis parameters due to the use of estradiol valerate, a prodrug of the natural human 17 β -estradiol instead of ethinyl estradiol. The estrogenic component used in this COC is therefore different from the estrogens usually used in COCs.

The claims of the MAH were based on a comparison to a triphasic EE/LNG-containing COC Triquilar . In this comparative study effects on SHBG levels and hemostasis parameters were shown to be lower. However, the triphasic COC Triquilar is not considered an adequate comparator for such comparisons, as it contains a higher amount of ethinyl estradiol (2nd week EE dose 40 micrograms) than standard COCs. The comparative study versus the monophasic LNG-containing COC, Miranova) did not show differences in increase in SHBG level between COCs. Furthermore, the clinical relevance of differences in SHBG increase is unknown.

Generally, hemostatic parameters were numerically lower for Qlaira compared to Microgynon 30. However, the clinical relevance of these minor differences in the absence of clinical data is unknown. However, it has to be taken into consideration that none of the haemostatic variables are validated surrogate parameters for the clinical endpoint of venous thrombosis. In conclusion, inclusion of this statement is considered not acceptable as the clinical relevance is unknown. The planned large comparative post-marketing safety surveillance study that will be conducted to assess the VTE risk of

Qlaira compared to other COCs in a non-selected target population is the only way to reliably assess the impact of estradiol valerate instead of ethinyl estradiol on VTE risk.

Effects on lipids

The MAH claims that in combination with dienogest, estradiol valerate displays an increase in HDL, while LDL-cholesterol levels are slightly decreased. Apart from the observation that in the comparative study versus microgynon (LNG-COC) no differences were noted, none of the COCs currently on the market have any statement regarding effects on lipids. In general, the clinical relevance of any effects on lipid metabolism induced by COC-use is unknown. The only relevance is the increase in triglycerides, demonstrated for all COCs, which may be of importance in women with high triglycerides levels or (family) history of pancreatitis, see general statement in SPCs of all COCs including Qlaira "*Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs*". In conclusion, inclusion of this statement is considered not acceptable as the clinical relevance is unknown.

In conclusion, contraceptive reliability of the Qlaira COC was shown to be adequate. Indirect comparison suggests contraceptive efficacy for Qlaira, within the range of that noted for COCs recently approved in the EU. A typical safety profile compared to other COCs is found for Qlaira. The claims on lower hepatic effects and lower impact on SHBG levels and hemostasis parameters cannot be justified due to unknown clinical relevance. The planned large comparative post-marketing safety surveillance study that will be conducted to assess the VTE risk of Qlaira compared to other COCs in a non-selected target population is the only way to reliably assess the impact of estradiol valerate instead of ethinyl estradiol on VTE risk.

IV OVERALL CONCLUSION

The first assessment report of the MEB was discussed in the Board meeting of 14 February 2008. The Board decided to follow the advice of the assessors. Questions on the choice of the dosages of both hormones and on potency differences of estradiol versus ethinylestradiol were added.

During the Decentralised Procedure a number of changes were introduced in the product-information because of the comments raised by the RMS in their assessment, but also because of the comments of the Concerned Member States. The major issues for discussion were the contribution of the endometrial changes to the contraceptive effect of Qlaira, the calculation of the Pearl Index, the bleeding data, the endometrial safety and the environmental risk assessment

At Day 210 agreement was reached between the member states and the MAH on product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling. The Decentralised procedure was finished on 14 October 2008

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure.

On the basis of the data submitted, the concerned member states have granted a marketing authorisation. Qlaira film-coated tablets from Bayer Schering Pharma AG was authorised in the Netherlands on 12 November 2008.

The SPC, package leaflet and labelling are in the agreed templates. Braille conditions are met by the MAH.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The PSUR submission cycle is 6-monthly during the first 2 years. Thereafter once a year for the following two years and thereafter at 3-yearly intervals. The international birth date (IBD) is unknown. The MAH is requested to inform as soon as possible the RMS and CMSs of the date of granting of the first marketing authorisation in the EU to determine the date for the first renewal.

Post-approval commitments

The following post-approval commitments have been made during the procedure.

Quality

- The MAH committed to provide the stability data of all Qlaira formulations covering the whole shelf-life when available.

Risk management plan

- The MAH committed that soon after the launch of Qlaira, a large comparative post-marketing safety surveillance study will be conducted to assess the VTE risk of Qlaira compared to other COCs in a non-selected target population, (INAS-EV) and a preferential prescribing monitoring program (observational study). The MAH will take care that unexpected market uptake or incidence rates will not violate the power of the post-marketing VTE and preferential prescribing studies.
- As outlined in the INAS-EV study protocol, the MAH committed to gather data on pregnancies, including data on return to fertility and pregnancy outcomes. The results of the INAS-EV study with data on return to fertility and pregnancy outcomes will be provided.
- As outlined in the INAS-EV study protocol, the MAH committed, that all women who receive a new prescription for a COC at the participating centers will be asked to participate in the study. Thus,

also women below the age of 18 years taking Qlaira will be included. The results of the INAS-EV study with data in adolescents below 18 years will be provided.

- The MAH committed to report the endometrial and cervical safety results of the two studies (308960 and 308961) conducted in women suffering from dysfunctional uterine bleeding after availability and prior to start of the forthcoming clinical phase IV comparative post-marketing safety surveillance study (INAS-EV) . A decision in what extent endometrial and cervical safety should be investigated in this study will be made on the endometrial and cervical safety results from the two studies (308960 and 308961).
- The MAH committed to report the safety results of the two studies (308960 and 308961) conducted in women suffering from dysfunctional uterine bleeding in the PSURs of Qlaira. The first PSUR is planned to have a data lock point six month after marketing authorization.
- The MAH committed to closely monitor endometrial safety with Qlaira in the postmarketing period. The evaluation of spontaneous reports, as well as reports from literature, clinical and observational trials on endometrial safety will be reported in PSURs.
- The MAH committed to submit a variation type II (new indication) after availability of an agreed pediatric investigational plan (i.e. approximately end of 2009 or later, depending on the progress of the procedure), if the efficacy results of the two studies (308960 and 308961) conducted in women suffering from dysfunctional uterine bleeding are favorable. At this point in time, the MAH will submit the efficacy data as well as the safety data supporting the new indication. When the indication dysfunctional uterine bleeding will be granted, the label will be updated accordingly.

Environmental risk assessment

For the completion of the environmental risk assessment (ERA) the MAH commits to perform the following studies and to update the environmental risk assessment :

Estradiol

Substance; study type	Start experimental phase	End experimental phase	End chemical analysis	Final report
Activated sludge respiration inhibition	September 2008	September 2008	September 2008	October 2008
Bioaccumulation fish	September 2008	October 2008	December 2008	January 2009

- The literature data on a full life cycle test with estradiol on the medaka (*Oryzias latipes*) published by Seki et al. 2005 will be used to support the environmental risk assessment of estradiol. Accordingly, the no-effect level determined in that study (3 ng/L) will be used to update the ERA of estradiol.

Dienogest

Substance	Start experimental phase	End experimental phase	End analytical chemistry and histopathology	Final report
Dienogest				
Aquatic-sediment test	June 2008	November 2008	March 2009	April 2009
Fish sexual development test (FSDT)	November 2008	January 2009	May 2009	June 2009
Short-term reproduction test	January 2009	March 2009	May 2009	June 2009

- If there are unexpected effects observed in the FSDT or short-term reproduction assay, the necessity to conduct a fish full life-cycle (FFLC) test will be further discussed.

- The ERA for estradiol and dienogest will be updated in the 3rd quarter in 2009 after the completion of the whole study programme.

List of abbreviations

AE	Adverse event
ALAT	Alanine aminotransferase
Alu	Aluminium
AP	Alkaline phosphatase
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CBG	corticoid binding globulin
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C _{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
COC	Combined oral contraceptive
CV	Coefficient of Variation
CYP	cytochrome P450
DNG	Dienogest
ECG	electrocardiograph
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
E2	17β-estradiol
EE	Ethinylestradiol
ERA	Environmental Risk Assessment
EU	European Union
EV	Estradiol valerate
FAS	Full analysis set
FFLC	Fish full life-cycle
FSDT	Fish sexual development test
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GPT	glutamic pyruvic transaminase
HDL	High-density lipoprotein
ICH	International Conference of Harmonisation
ITT	Intention to Treat
LDL	Low-density lipoprotein
LDPE	Low Density Polyethylene
LNG	Levonorgestrel
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
NF	National Formulary
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PI	Pearl Index = (number of unintended pregnancies / number of women years) x 100
PIA	Adjusted Pearl Index
PIU	Unadjusted Pearl Index
PL	Package Leaflet
PPS	Per-protocol set
PSUR	Periodic Safety Update Report
PVC	Poly vinyl chloride
RH	Relative Humidity

SD	Standard Deviation
SHBG	sex hormone binding globulin
SPC	Summary of Product Characteristics
$t_{1/2}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States
VTE	venous thromboembolism

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached