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M E B

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Visanne, tablets, 2 mg
Bayer BV, The Netherlands

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/1569/001/DC
Registration number in the Netherlands: RVG 104058

3 March 2010

Pharmacotherapeutic group:	Progestagens
ATC code:	G03D
Route of administration:	oral
Therapeutic indication:	treatment of endometriosis
Prescription status:	prescription only
Date of authorisation in NL:	21 December 2009
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 Visanne, 2 mg tablets, from Bayer BV, The Netherlands. The date of authorisation was on 21 December 2009 in the Netherlands. The product is indicated for treatment of endometriosis.

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

Endometriosis is the growth of endometrium outside the uterine cavity or myometrium (endometriotic implants), usually in the peritoneal cavity, which induces a chronic, inflammatory reaction. The hormonal status of a woman is essential in the development and maintenance of endometriosis. Endometriotic tissue is dependent on estrogen for survival and growth, while ovarian hormonal secretion is dependent on the functionality of the hypothalamic- pituitary-ovarian axis. Endometriosis presents either with infertility or pelvic pain, including dysmenorhea, dyspareunia, pelvic pain not associated with the menstrual cycle, and dysuria. The condition is predominantly found in women of reproductive age, with a prevalence of 5-10%. Definite diagnosis requires visualization (usually laparoscopy) with biopsies for histological verification.
Current treatment is surgery (laparoscopic ablation) in severe cases and patients desiring pregnancy. Medical (hormonal) treatments are GnRH agonists, Danazol, synthetic progestagens (most commonly medroxyprogesterone) and combined oral contraceptives (not approved for this indication).

Dienogest is a nortestosterone derivative with no androgenic but rather an antiandrogenic activity of approximately one third 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*.

Dienogest acts on endometriosis by reducing the endogenous production of estradiol and thereby suppresses the trophic effects of estradiol on both the eutopic and ectopic endometrium. When given continuously, dienogest leads to a hypoestrogenic, hypergestagenic endocrine environment causing initial decidualization of endometrial tissue followed by atrophy of endometriotic lesions.

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-clinial and clinical data.
The active component of Visanne is considered to be well-known and the clinical pharmacology of dienogest has been extensively studied. Parts of the data in the dossier of Visanne were already submitted in the dossiers of the fixed combination of estradiol valerate 2 mg and dienogest 2 mg (Climodien, NL License RVG 24830), the lower dosed medicinal product of estradiol valerate 1 mg and dienogest 2 mg (Climodien 1/2 , NL License RVG 30401), and Qlaira (NL License RVG 101491). However, these products are approved for another indication, respectively hormone replacement therapy in postmenopausal women and as oral contraceptive.
Dienogest in combination with ethinyl estradiol (EE) is marketed since 1995 in the indication 'oral contraception' under the trade name Valette®/Celimona® in some EU countries, among others Germany, but not in the Netherlands.

There is no EU guideline on the development of medicinal products for the treatment of endometriosis.
An application based primarily on the comparator-controlled study AU19 to demonstrate efficacy of Visanne has been submitted on 17 January 2001 to the Medicines Evaluation Board (MEB) in a national procedure with the intention to start a Mutual Recognition Procedure (MRP) subsequently.
The application was withdrawn on 15 July 2003 as Study AU19 was rated not sufficient to demonstrate efficacy of Visanne in relieving endometriosis-associated pelvic pain (EAPP). The non-inferiority study design in the absence of a placebo arm in pain due to endometriosis is not justified, as the efficacy of the comparator in endometriosis-associated pain (assay sensitivity) was not established in placebo-controlled trials.
The second objection – on vaginal bleeding data – was considered solved by the MEB at that time. The placebo-controlled study (study A32473) was started subsequently as requested by the MEB. A pre-

submission meeting with the MEB was held on 14 August 2008. The proposed changes in presentation of the statistical methods were accepted and minor improvements were suggested. The proposed method for presenting the safety data was accepted.

For the development of the product in the paediatric population the company has submitted a paediatric investigation plan (EMEA-000147-PIP01-07). The PDCO granted a positive opinion on the paediatric investigation plan during the September 2008 meeting. The positive opinion on the paediatric investigation plan covers the subset girls from menarche to less than 18 years. A deferral has been granted for initiation and completion of the studies in this subset. The Paediatric Committee (PDCO) also granted a waiver which applied to boys from birth to less than 18 years and to pre-menarcheal girls on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subsets.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance

General information
The active substance is dienogest; an established active substance, not described in a Pharmacopoeia. The active substance is practically insoluble in water, slightly soluble in ethanol and ethyl acetate, sparingly soluble in acetone and methanol and freely soluble in dimethylsulfoxide. Dienogest is a synthetic steroid hormone with four chiral centers. Dienogest does not exhibit polymorphism.

Manufacturing process
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/EMEA 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. Dienogest is synthesized in three chemical modification steps and one purification step. The structure, other characteristics and quality control of dienogest are described in the MAH's part of the DMF which is part of the Module 3, too.
The limits for all residual solvents are tighter than the ICH requirements. The limit for any individual impurity is in line with the Ph.Eur. monograph Substances for pharmaceutical use. The limit for total impurities is based on batch analyses results.

Quality control of drug substance
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.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for three production scaled batches.

Stability of drug substance
Stability data on the active substance have been provided for three full scaled batches stored at 25°C/60% RH (5 years) and 30°/65% RH (5 years) and 40°C/75% RH (6 months). The batches were

adequately stored. 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 drug product is a white round tablet with an embossed “B” on one side and a diameter of 7 mm containing 2 mg Dienogest. The excipients are potato starch, lactose monohydrate, microcrystalline cellulose, Povidone, talc, magnesium stearate and Crospovidone. The drug product is packed in green transparent PVC/Al blisters to protect from light. 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 particle size of the drug substance is limited as 100% is < 30 µm and > 99% is < 20 µm. The impact of the particle size of Dienogest on in-vitro dissolution and the impact of the amount of binder, disintegrant and lubricant on hardness, friability, disintegration time, dissolution rate and content uniformity have been investigated. Wet granulation is chosen as the manufacturing process. The choice of container closure system is justified. The pharmaceutical development of the product has been adequately performed. The development of the clinical batches has been discussed adequately and the clinical batches are found to be representative for the batches to be marketed.
The stirring speed, choice of medium and the discriminating nature of the dissolution method have been justified. Placebo batches were used for the development of the manufacturing process. As only 2 mg of active substance is present in the formulation, no significant changes are to be expected for the physical parameters of the tablets.

Manufacturing process
The drug product was manufactured by wet granulation. The granulate is compressed and the tablets are packed. Holding times of the mixture (4 weeks) and the bulk tablets (12 months) are justified with stability data. The provided in-process controls are deemed acceptable.
The manufacturing process has been adequately validated according to relevant European guidelines on three production scale batches. The product is manufactured using conventional manufacturing techniques, but given the low concentration of active substance in the drug product, the manufacturing process can be considered as non-standard.

Excipients
The excipients comply with their respective Ph.Eur. monographs. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identity, disintegration, dissolution, assay, related substances, uniformity of dosage units and microbial contamination. The shelf-life specifications are identical to the release specification, except for the omission of the tests on identification and uniformity of dosage units, and different limits are applied for related substances during release and at the end of shelf-life. A specification for water content was not included. During the manufacturing process the granules are controlled on water content. However, because no trend analysis could be performed on the results of batches during development, the applicant commits to include a test on water content in the next scheduled stability study and include limits for water content in the drug product specifications when trends are observed for water content in this study. The analytical methods have been adequately described and validated. The stability indicating nature of the assay and related substances methods should be demonstrated.
Batch analytical data from the proposed production site have been provided on ten full production scaled batches, demonstrating compliance with the release specifications.

Stability of drug product
Stability data on the product have been provided on three full production scaled batches, manufactured in 2000, stored at 25°C/60% RH (5 years), 30°/70% RH (5 years) and 40°C/75% RH (6 months) and three

full production scaled batches, manufactured in 2003/2004, stored at 25°C/60% RH (up to 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 green PVC/Al blisters.
The batches manufactured in 2000 show a different stability profile from the batches manufactured in 2003/2004 and are therefore not accepted as supporting batches. The results of the 2003/2004 batches demonstrate an increase in related substances. No clear trends could be observed for assay or any other parameter. Trend analysis should be performed for water content in the next stability study.
A photostability study has been performed in accordance with the NfG on photostability testing, ICH Q1B. The results clearly demonstrate that the drug product is light sensitive and that the green coloured blister packaging protects the tablets from light. The proposed shelf-life of 60 months without specific storage conditions when stored in the original packaging to protect from light can be granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
A TSE declaration has been provided by the MAH for lactose monohydrate as it is of animal origin. 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).
Only one metabolite tested, the aromatic metabolite of dienogest, showed any binding and activity at the steroid receptors tested. Due to the low plasma levels at which this metabolite is present in humans, a significant estrogenic activity of this metabolite is not anticipated.
In vitro studies showed dienogest-induced inhibition of cell proliferation in endometrial stromal cells and in cells isolated from endometriotic lesions.
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 antiovulatory 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 antiprogestional properties. Dienogest as compared to levonorgestrel has stronger estrogenic activity. Dienogest has marginal androgenic effects as compared to 3-keto-desogestrel. Dienogest 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. It can be concluded that dienogest at therapeutic relevant doses may not induce unwanted effects in women.
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 hr and in rhesus monkeys 1-2 hr (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 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, 87-93% in dogs, 91-92% in baboons and 93-94% in human.
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 dienogest, 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 dienogest 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.
The data available are sufficient to permit conclusions regarding biotransformation in rat, monkey and human, but there are no valid data to draw clear conclusions on biotransformation in the other test species. 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 t1/2 for total plasma radioactivity in the range of 7-13 hrs, whereas dienogest is eliminated from the plasma with t1/2 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. There was evidence for enterohepatic circulation, based on the plasma concentration versus time curve in rats and mice.

Pharmacokinetic drug interactions
No effect on the CYP family of enzymes by dienogest is expected.

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 studies are of low quality with respect to performance of the studies and/or reporting. The values on C_{max}, T_{max} and AUCs are suggestive for species differences.
Conclusions on linearity cannot be drawn on the results from the single-dose studies. Because of the good quality of the pharmacokinetic parameters in the toxicity studies it was not considered 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. T_{max}, C_{max} and the AUC remained approximately constant in the tested dose ranges (i.e. 2-100 mg/kg bw/d in mice, 0.1-10 mg/kg bw/d in Rhesus monkeys, 0.4-10 mg/k in cynomolgus monkeys).
Conclusions on dose-proportionality are based on the multiple-dose experiments. 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 months studies in both sexes, with doses 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 brome sulftalein were found. Some effects on serum cholesterol (decrease) and free fatty acids (increase in one year study) and blood clotting factors (in general without effects on blood clotting function) 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 (prolacting-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. Retention of brome sulftalein was slightly prolonged indicating a slight effect on liver function. Males showed the following effects: decrease of prostate weight, unilateral hypoplasia of testes, hyperplasia of mammary glands. In addition, increase in serum protein and β-lipoprotein fraction was found. The histological changes were found in the liver. 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.

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 for 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 (mouse lymphoma cells), UDS assay (primary hepatocytes) and the chromosomal aberration test (Chinese hamster lung cells and human lymphocytes). *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
Four carcinogenicity studies with dienogest were conducted, one in the mouse and three 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 18 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 dose levels of dienogest were quite low; the highest dose did not exceed the human intake based on AUC levels. Further, effects on the endometrium were not reported.
The second rat study (B398) observed neoplastic changes in male rats, i.e. 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 body weight, which is a factor 36 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.
The third rat carcinogenicity study (Report A04494) was performed fully under GLP. The compound was administered by oral gavage. There were no statistically significant differences in mortality and survival times between the groups. Tumour incidences were not significantly different between the groups. The high dose of 10 mg/kg/day dienogest in this study was approximately 10 times the human AUC.
Taken together, the results of the carcinogenicity studies did not indicate an unexpected tumorigenic response to long-term dienogest administration in mice or rats.

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 (e.g. by dose-related thymic involution in rats; slight broadening of the thymic cortex in dogs, dose-related increase in total lymphocytes in peripheral blood) was suggested in a published report which could not be assessed. In functional assays in mice, it was observed that 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 provided 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
The MAH has provided an Environmental Risk Assessment dated April 2008. This risk assessment was also submitted as part of the dossier for Qlaira. It was agreed that the MAH could submit an updated environmental risk assessment as a follow up measure in February 2010, together with a new update for Qlaira.

II.3 Clinical aspects

Quality of clinical studies, compliance with GCP
The MAH declares that -except for the early pre-GCP studies (studies A01177, A01176, and some phase 1 studies)- all clinical studies performed in the framework of this submission were conducted in accordance with GCP, the principles of the Declaration of Helsinki, and all applicable national regulations valid at the time the studies were performed. The protocols and protocol amendments were reviewed and approved by Independent Ethics Committees or Institutional Review Boards. The early pre-GCP studies were conducted in accordance with all applicable national regulations valid at the time the studies were performed and according to best scientific practice.

II.3.1 Pharmacokinetics

Absorption
Absolute Bioavailability
The absolute bioavailability of dienogest was estimated by comparing doses of 2 mg/subject after intravenous and oral (as a tablet) administration under fasting conditions.
The results indicate that the absolute bioavailability of dienogest is 90.5% with a confidence interval of 86% - 95%.

Influence of food
The influence of a high-fat breakfast on the bioavailability of dienogest from the tablet with 2 mg dienogest was investigated. Also a comparison was made with a microcrystalline suspension in a three-way crossover study in 24 healthy young volunteers. In the table below the results of this study are summarized.

Table 1 Pharmacokinetic parameters of dienogest after oral administration of 2 mg tablets under fasting and fed conditions and an oral 2 mg microcristalline suspension (n = 24; arithmetic mean ± s.d., for t_{max} : median and range)

	tablet Fasted	tablet Fed	Microcristalline suspension
AUC_{0-48h} (ng.h/ml)	438 ± 123	453 ± 133	4427 ± 129
AUC_{0-inf} (ng.h/ml)	453 ±135	469 ± 147	441 ± 136
C_{max} (ng/ml)	40.9 ±11.0	37.9 ± 6.7	46.2 ± 8.9
T_{max} (h)	1.75 (0.67 – 4.0)	2.0 (0.67 – 6.0)	0.67 (0.33 – 1.5)
$T_{1/2}$ (h)	8.9 ±1.7	8.9 ±1.8	8.7 ± 1.6

The extent of absorption after administration of the tablet in fasted state compared with the micronized suspension was 100% (90% CI 0.95 – 1.06).
The influence of food on the bioavailability was small. The 90% CI was for the AUC 0.95 – 1.04 and for the C_{max} 0.85 – 1.04.

Distribution
Drug binding
Plasma protein binding was performed *in vitro* by ultrafiltration with ^{3}H-labeled dienogest and increasing amounts of non-labelled dienogest in the range of 100 to 1000 ng/ml. In addition, the plasma protein binding of dienogest was investigated in ex vivo samples obtained at several times after repeated oral

administration of of a combination of 2 mg dienogest and 0.03 or 0.05 mg ethinylestradiol. A fraction of 10% of circulating DNG is present in the free form with approximately 90% being bound non-specifically to albumin. Testosterone was not displaced from its plasma protein binding by dienogest. Dienogest does not bind to SHBG, so the pharmacokinetics will not be influenced by increasing SHBG as consequence of estradiol administration.

Metabolism and excretion

Attempts were made to elucidate the metabolism of dienogest. Urine and plasma were sampled after oral administration of ^{3}H-labeled dienogest (0.1 mg/subject) to five young healthy women (see also under Pharmacokinetics after single dose). Following conjugate hydrolysis 78% of radioactivity excreted in pooled 48 h urine was extractable (Amberlite XAD and ether extraction) as follows: free steroids 30%; "glucuronide" fraction 25% and "sulphate" fraction 22%. The percentage of unchanged dienogest in the fraction of free steroids, determined via thin layer chromatography, was approx. 1% of the total radioactivity in urine. The other part remained in the urine or in washing waters of the extracts.

In a further investigation the metabolic profile in urine and plasma of the same subjects after oral administration of 2 mg ^{3}H-dienogest was determined. The concentration of the total radioactivity in plasma samples derived from a sample taken 12 h post dose was 20 ng-eq /mL; the excretion into 48h urine amounted to 62% of the administered dose. From these plasma and urine samples the extractable radioactivity was 93 and 56%, respectively, of the total radioactivity and was distributed between the fractions as follows:

Table 2

	Plasma	Urine
Free steroids	55%	20%
Glucuronides	24%	23%
Sulphates	14%	14%
Not identified	7%	43%

The metabolic profile of dienogest is very complicated. The chemical structure of dienogest, in principle, makes a variety of potential biotransformation reactions possible like hydroxylation of double bonds, alteration of the 17α-side chain with nitrogen elimination which can partially combine together. A series of metabolites has been isolated from urine. The mass spectra and UV absorption provided evidence on principal pathways of dienogest biotransformation being: hydroxylation; introduction of additional double bonds originated possible from dehydration of hydroxylated compounds; aromatisation of the A-ring; elimination of nitrogen from the 17α-side chain; hydroxylation + reduction of the oxo group or hydrogenation of a double bond and reduction of the oxo-group or/and hydrogenation of a double bond. At least 9 metabolites were isolated from the fraction of free steroids in urine, however, no quantitative data were submitted.

Pharmacokinetics after single dose

The pharmacokinetics after single oral and i.v. administration of dienogest in five healthy female subjects (aged 30 – 38 years) who received intravenously 79 – 85 μg and orally 101 μg ^{3}H-labeled dienogest as a single dose is given in the table below.

Table 3

	Total radioactivity		Free fraction of steroids	
	i.v.	oral	i.v.	oral
$T_{1/2}$ (h)	12.6 ± 2.5	11.7 ± 1.8	9.0 ± 2.7	8.4 ± 1.4
V_{ss} (L)	45 ± 13		52 ± 17	
$AUC_{0\text{-}24h}$(% dose.h/L)	28.7 ± 4.4	27.6 ± 5.1	20.2 ± 2.7	20.1 ± 4.6
Cl_{tot} (mL/min)	32.6 ± 4.7		54 ± 16	
Ae $feaces_{5d}$ (% dose)	13 ± 1.5	11 ± 1.1		
Ae $_{24h}$ urine(% dose)	51 ± 4.0	54 ± 5.3		
Ae $_{5d}$ urine (% dose	68 ± 7.9	72 ±6.4		

The pharmacokinetics after oral and intravenous administration is comparable for the total radioactivity as well as for the free fraction. It is also clear that about 100% of the dose is absorbed after oral administration and the major route of excretion is by urine for both administration routes. Unchanged dienogest was not measured in this study. After oral administration peak plasma of total radioactivity and free steroids concentrations were reached within 2 hours upon administration.
The ratio between radioactivity in whole blood and plasma was after oral administration 1.6 and after i.v. 1.4, so no substantial binding to erythrocytes could be detected.
Several metabolites of dienogest were found in different species and biological materials but no major peaks were found in human plasma beside unchanged dienogest.
The metabolites do probably not contribute in a relevant way to the effects of dienogest. The aromatic dienogest metabolite showed estrogenic activity as well as slight antiprogestogenic activity but this metabolite was only important in rats, but could not be detected in a relevant amount in human and monkey plasma.

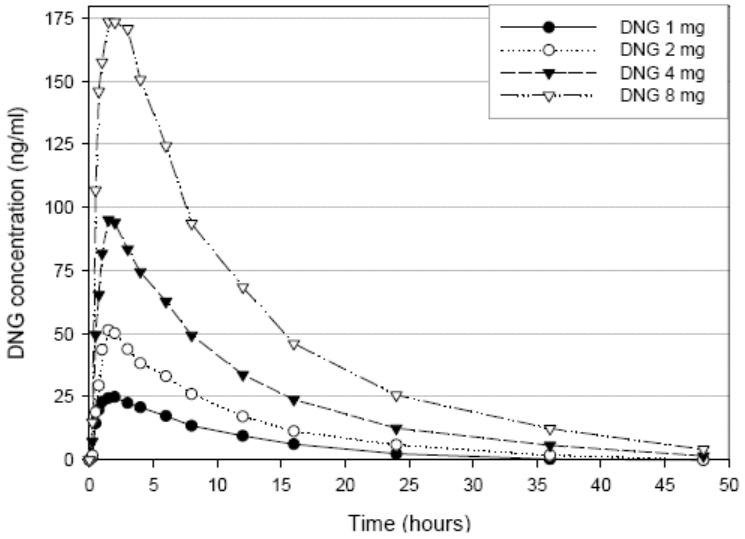
In a study ^{3}H-labeled dienogest was administered as single oral dose (0.1 mg/kg) to five female volunteers. In plasma the pharmacokinetics of total radioactivity and dienogest was estimated. Also the metabolic profile in urine was investigated (see under Metabolism and Excretion).

Table 4

	Total radioactivity	Radioactivity as unchanged dienogest
$AUC_{0\text{-}24h}$ (ng.eq.h/mL)	1637 ± 242	988 ± 343
$AUC_{0\text{-}inf}$ (ng.eq.h/mL)	3314 ± 614	1271 ± 473
C_{max} (ng.eq/mL)	106 ± 16	75 ± 21
C_{24h} (ng.eq/mL)	42 ± 7	19 ± 8
C_{48h} (ng.eq/mL)	15 ± 5	3.7 ± 2.4
$T_{1/2}$ (h)	21 ± 5	9.7 ± 2.3
Cl_{tot} (l/h)	1.82 ± 0.24	5.37 ± 1.57
T_{max} (h)	3 – 8	

The results demonstrate that the concentration of total radioactivity is nearly three-fold of that of dienogest. The clearance of the metabolites is slower than that of the parent compound. All studies after single dose show comparable results.

Dose proportionality
The linearity of the pharmacokinetics of dienogest was investigated in the range of 1 to 8 mg tablets in 12 healthy women. The mean concentration-time curves of dienogest after oral administration of different doses to healthy female volunteers are presented in the figure below.



The pharmacokinetics of dienogest after single-dose administration of 1 to 8 mg is linear in all aspects. No studies on the linearity after multiple doses are submitted.

Pharmacokinetics at steady state
The pharmacokinetic variables of dienogest after 2 mg dienogest tablet as a single dose and after repeated dose for 14 days are given below (Arithmetic means ± s.d.. For tmax: median and range)

Table 5

	Single dose	Repeated dose
AUC_{0-24h} (ng.h/ml)	441 ± 92	547 ± 129
AUC_t (ng.h/ml)	519 ± 137	666 ± 195
AUC_{0-inf} (ng.h/ml)	535 ± 138	682 ± 205
C_{max} (ng/ml)	47.6 ± 8.7	52.2 ± 8.3
$t_{1/2}$ (h)	9.4 ± 1.9	10.2 ± 1.8
t_{max} (h)	1.5 (0.67 – 3.0)	1.25 (0.67 – 6.0)

The mean accumulation factor estimated in this study is about 1.25. This can be expected for a compound with a half life of 10 hours. So no unexpected accumulation occurs with dienogest in steady state.

Comparison of trial formulations with the product to be marketed
Most formulations used in the clinical trials are identical with the product to be marketed.

Effect of estradiolvalerate on dienogest
The bioavailability of dienogest is not affected by co-administration of estradiol valerate. The residual coefficients of variation found in the study are small indicating a small intra-individual variability in the pharmacokinetics of dienogest.

Medicinal products used for other indications
The results from one study demonstrated a clinically significant drug interaction between rifampicin and dienogest /17β-estradiol combinations. Co-administration of rifampicin with 2 mg estradiolvalerate / 3 mg dienogest led to significant decreases in steady state concentrations (50% and 25% for dienogest and 17β-estradiol, respectively) and systemic exposures (80% and 40% of dienogest and 17β-estradiol, respectively), which will affect the contraceptive efficiency of estradiolvalerate/dienogest in a clinical significant way.
A study evaluates the effect of CYP 3A4 inhibitors, ketoconazole and erythromycin, on the steady state PK of estradiolvalerate and dienogest. The results show that the exposure to dienogest increases almost three fold after concomitant administration of ketoconazole. This effect is somewhat lower with erythromycin. This confirms the result with the inducer rifampicin, i.e. dienogest is metabolised by CYP 3A4.

Influence dienogest on nifedipine pharmacokinetics
The influence of dienogest on the pharmacokinetics of nifedipine as model substrate for CYP 3A4 metabolism, was investigated. No differences were found between treatments with or without dienogest on the pharamcokinetics of nifedipine, indicating that dienogest does not affect CYP 3A4 metabolic system. This confirms the *in vitro* studies on metabolism of dienogest with respect to P450 enzymes.

Special groups
**Impaired renal function*
After administration of dienogest about 63% of the dose administered is excreted by urine in the first 48 h of which 20% as unconjugated steroids and 1% as unchanged drug. However, no studies including patients with renal impairment are submitted.
Therefore, it is recommended to add a statement that pharmacokinetics of Visanne is not investigated in patients with renal insufficiency in section 5.2 of the SPC. Pharmacokinetic properties and to maintain the remark on patients with severe renal insufficiency in section 4.4 Special warnings and special precautions for use.

**Hepatic impairment*
It is stated that Visanne is contra-indicated for patients with “acute of chronic liver disorder resulting in unresolved liver function disturbances”. Therefore, the drug should not be administered to patients with hepatic impairment.

**Elderly*

The pivotal pharmacokinetic studies (single and multiple-dose studies) and clinical studies are conducted in postmenopausal women aged 45 – 75 years (for the Climodien indication) as well in healthy young female subjects (for the Qlaira indication). No differences in pharmacokinetics were observed between healthy young female subjects and postmenopausal women.

II.3.2 Pharmacodynamics

The pharmacological profile of dienogest is well known. Some of the pharmacodynamic studies were already conducted decades ago.

Determination of endometrial transformation dose

The progestagenic effect of dienogest was assessed in (natural or surgical) postmenopausal women, receiving 50 µg Ethinylestradiol per day over 12-14 days followed by a combination of 50 µg Ethinylestradiol + 0.1, 0.25, 0.35, 0.45 or 0.55 mg dienogest per day over 14 days. The transformation dose was found to be 6.3 mg per cycle, i.e. 0.45 mg per day for 14 days. A daily dose of 0.45 mg dienogest in postmenopausal women (with ethinylestradiol primed endometrium) induced endometrial transformation (study B468) .

In other studies determination of the endometrial transformation dose of dienogest in ethinylestradiol primed postmenopausal or ovariectomized women revealed transformation of endometrium as assessed by histological examination during day 15 and 29. Despite a progestagenic effect at doses from 0.25 to 0.55 mg for 14 days, an exact transformation dose could not be defined in study A03128.

Hormone analytical results of 21 subjects (who all ovulated in the preceding cycle), of whom 12 completed two dosing cycles, revealed that dienogest ≥ 1.0 mg/day inhibits ovulation and 0.5 mg does in two-third of women. However, follicular growth, even on 2 mg dienogest, is not completely suppressed as can be concluded from serum estradiol levels. As known for progestin-only products an increase in the occurrence of breakthrough bleeding occurs during treatment with dienogest but the duration of bleeding is reduced on average from 5.5 days to 3.8 days at a dose of 2 mg dienogest (study B470)

The effects of 2 mg dienogest on hypophyseal gonadotropin secretion and their hypothalamically determined pulsatile character were examined in 7 healthy female volunteers with normal cycles aged 21-32 years. It appeared that 2 mg dienogest per day inhibits ovulation, but ovarian hormone production is not completely suppressed (study A02263).

QT-prolongation study

No indication of QTcF prolongation was seen even during supra-therapeutic dose of 10 mg dienogest/day (study A35653).

Conclusion

The overall conclusion on pharmacodynamics is that dienogest at doses ≥1.0 mg/day inhibits ovulation, as 2 mg/day a fortiori does. None of the volunteers ovulated, and follicular growth was stopped at a size of 10 mm. Consistent herewith follicular growth and serum E2 levels were not completely suppressed with the dose of dienogest (2 mg/day), the dose proposed in this application procedure. Nevertheless, pharmacodynamic data have shown that the estradiol levels are suppressed and are well below the threshold of 100 pg/ml (mean 55.3 pg/ml, 95%CI: 44.5 to 66.1 pg/ml), which is considered the threshold at which "(…) endometriosis lesions will grow, causing pelvic pain (…)" (Barbieri 1998).

II.3.3 Clinical efficacy

The main clinical program comprises of 4 clinical Phase 2/3 studies in the treatment of endometriosis: one dose-response study (A02266) to evaluate effects on reduction of endometrial lesions by means of laparoscopy, and three clinical phase 3 studies were conducted to demonstrate efficacy of Visanne in the **treatment of Endometriosis-associated pelvic pain (EAPP)** using a VAS (visual analogue scale) of which one was an open extension phase of 52 weeks.

Study **A02266** was an open, randomized phase 2 dose-finding study to assess the efficacy of Visanne in comparison to 1 and 4 mg dienogest. This study is considered the pivotal study to demonstrate the efficacy based on the reduction of endometriotic lesions by means of laparoscopy using the rAFS score.

Study **A32473** was designed to demonstrate superiority of Visanne compared to placebo and study **AU19** to demonstrate non-inferiority of Visanne in comparison to the GnRH agonist leuproreline acetate (LA). The third study (**A39700**) (treatment duration 52 weeks) is an uncontrolled extension of study A32473 to evaluate menstrual bleeding patterns and demonstrate sustained reduction of EAPP during long-term treatment with Visanne.

Two other studies (**A01177** and **A01176**) were performed to demonstrate the efficacy based on the reduction of endometriotic lesions by means of laparoscopy but these are early pre-GCP studies, so their outcomes can be considered as supportive data only. There are two additional clinical studies (**B567** and **A04431**) with different study populations or dosage.

Table 6: overview of efficacy studies

Study (protocol no.) Phase	Primary efficacy endpoint	Design	Treatment and total number of women by treatment group (full analysis set)	Treatment duration	End of study period
Efficacy studies – improvement of EAPP					
A32473 (307041) Phase 3	EAPP (assessed by VAS & change in rescue medication)	Multicenter, double-blind, randomized, placebo-controlled, parallel-group	Visanne: 102 Placebo: 96	12 weeks	2006
AU19 (97085) Phase 3	EAPP (assessed by VAS)	Multicenter, open-label, active-controlled, randomized, parallel-group	Visanne: 120 LA: 128	24 weeks	2001
A39700 (307059) Phase 3 (follow-up of study A32473)	EAPP (assessed by VAS) [a]	Multicenter, open, one-arm	Visanne: 168	52 weeks	2007
Efficacy studies – reduction of endometriotic lesions					
A02266 (JPH03992) Phase 2	Reduction of endometriotic lesions assessed by laparoscopy (rAFS score)	Multicenter, open, randomized, dose-controlled, parallel-group	DNG 1 mg: 4 [b] Visanne: 29 DNG 4 mg: 35 [c]	24 weeks	1996
A01177 (n.a.) Phase 2	Reduction of endometriotic lesions assessed by laparoscopy (EEC) [d]	Monocenter, open, uncontrolled	DNG 2 mg (2 x 1 mg): 104	24 weeks	1988 (date of report)
A01176 (n.a.) Phase 3	Reduction of endometriotic lesions assessed by laparoscopy (EEC) [d]	Multicenter, open, active-controlled, parallel-group	DNG 2 mg (2 x 1 mg): 119 NETA 10 mg (2 x 5 mg): 48	24 weeks	1991 (date of report)

n.a. = not applicable
a In the original study report, this parameter was a secondary endpoint because bleeding patterns were assessed as primary variable.
b Note: this group was prematurely discontinued due to increased occurrence of irregular vaginal bleeding (according to Amendment 2 of 1 Oct 1994).
c During integration of study A02266 into the pooled safety data base, it was found that one of these patients actually received no study medication. This patient was therefore excluded from the analyses prepared in the context of this submission, while she was included in the original analysis on which the study report is based. As a consequence, the total number of patients in the 4 mg DNG group is 35 or 34 depending on the respective source data.
d At baseline, the endoscopic endometriosis classification (EEC) according to Semm was used which was a commonly used scoring system for endometriosis before the rAFS score became the global standard

Dose selection

The one dose response study (A02266) , evaluating 2 and 4 mg dienogest, indicated that 2 mg dienogest is the lowest effective dose to reduce endometriotic lesions as assessed by laparoscopy using the rAFS scores. The 1 mg dose was discontinued early due to bleeding problems.

Table 7: Stages of endometriosis (rAFS) at baseline and after 24 week treatment, study **A02266**

Laparoscopy finding	Visanne		4 mg DNG	
	Baseline N = 29 (100.0%)	Week 24 N = 21 (100.0%)	Baseline N = 35 (100.0%)	Week 24 N = 30 (100.0%)
No endometriosis	0 (0.0%)	5 (23.8%)	0 (0.0%)	6 (20.0%)
Stage I	10 (34.5%)	11 (52.4%)	15 (42.9%)	15 (50.0%)
Stage II	11 (37.9%)	2 (9.5%)	12 (34.3%)	8 (26.7%)
Stage III	8 (27.6%)	1 (4.8%)	8 (22.9%)	1 (3.3%)
Missing	0 (0.0%)	2 (9.5%)	0 (0.0%)	0 (0.0%)

Note:

- During integration of Study A02266 into the pooled safety database, it was found that one of these patients actually received no study medication. This patient was excluded from the analyses in the context of this submission. As a consequence, the total number of patients in the 4 mg dienogest group is 35 or 34 depending on the respective source data.
- rAFS classification: stage I (minimal) = 1-5 points; stage II (mild) = 6-15 points; stage III (moderate) = 16-40 points; stage IV (severe) > 40 points
- The percentages refer to the number of patients with post-treatment laparoscopy findings available, i.e. 21 in the Visanne and 30 in the 4 mg dienogest group.

With both tested dose groups of dienogest, i.e. Visanne (2 mg/day) and 4 mg/day, a significant reduction of the rAFS score was observed after 24 weeks of treatment. The results did not suggest any benefit of the higher dose.

Table 8: Laparoscopic endometriosis score (rAFS) before and after treatment in study A02266

Treatment	rAFS score (mean ± SD)		Wilcoxon Signed Rank Test
	Baseline	Week 24	
Visanne	11.4 ± 9.2	3.6 ± 5.1	p<0.001
4 mg dienogest	9.7 ± 7.9	3.9 ± 4.4	p<0.0001

Efficacy in endometriosis-related pelvic pain

Pivotal efficacy study A32473

This was a multicenter, double-blind, randomized, placebo-controlled, parallel-group trial designed to prove superiority of Visanne in the treatment of EAPP in comparison to placebo. The double-blind treatment phase consisted of 12 weeks of consecutive treatment. Patients of study A32473 were offered further participation in a multicenter, open, one-arm 52-weeks follow-up study with continuous Visanne treatment (study A39700) to evaluate long-term efficacy and safety with Visanne.

The placebo-controlled design was considered the preferred approach for the primary endpoint of endometriosis related pain, as assay sensitivity for a non-inferiority design versus an active control (study AU19) in an earlier assessment by the Dutch MEB was considered not established in the absence of suitable placebo data.

Rationale of the primary endpoint “treatment of EAPP”:

The newly introduced primary efficacy variable “endometriosis associated pelvic pain (EAPP) evaluated by VAS”, is preferred by MAH above golden standard of laparoscopic evaluation of endometriotic lesions

before and after treatment using the rAFS score. The arguments of the MAH in support of this choice are that the main clinical symptom of the disease, i.e. pelvic pain, does not necessarily correlate with the extent and volume of endometriotic lesions as documented during laparoscopy. It might be that though endometriotic lesions that appear similar on visual inspection might cause different degrees of pain depending on the depths of their infiltration and their proximity to nerve fibers. In addition in recent years studies to demonstrate efficacy in the treatment of endometriosis were increasingly based on endpoints that are considered more relevant to the patient, like pelvic pain, considering that from a patient's point of view symptoms of pelvic pain are the mainstay of endometriosis. Therefore, the MEB is of the opinion that the primary endpoint could be accepted as a clinical relevant endpoint.

General inclusion/exclusion criteria
Patients between 18 and 45 years of age with pain associated with histologically-proven endometriosis (stages I to IV), as determined by diagnostic laparoscopy or laparotomy.
The threshold for pelvic pain score was a minimum 30 mm on the VAS at Screening and Baseline.

Main exclusion criteria included pregnancy or breast feeding, before menarche or after menopause, amenorrheic cycles ≤ 3 months prior to study start, therapy-resistant endometriosis; surgical therapy; need for primary surgical treatment of endometriosis, previous use of hormonal agents including GnRH agonists within 6 months, progestin and danazol within 3 months or oral contraceptives within 1 month prior to screening; any arterial/venous conditions, and depression in the last year.

Primary efficacy variables:
Individual absolute change of EAPP, as determined by ***change of VAS*** (in mm) and ***change of intake of rescue medication*** (cumulative over the preceding 28 days) between baseline and end of treatment (week 12).

Key secondary variables:
- Percentage of responders (50% and 75% reduction in EAPP)
- VAS adjusted for use of rescue medication

Statistical plan
- Placebo-controlled study**:**

Statistical analyses of the co-primary endpoints of change in VAS and rescue medication were based on the assumption that the intake of ibuprofen as rescue medication could potentially confound the measurement of pelvic pain using the VAS. For example, an improvement in pelvic pain VAS could be caused by the treatments' efficacy, an increased intake of rescue medication, or both. Therefore, both endpoints VAS and intake of rescue medication were planned to be analyzed simultaneously.

To account for the multiple endpoints selected (VAS and rescue medication), the 3-step hierarchical testing procedure of Roehmel et al. (2006) was employed. The testing procedure according to Roehmel et al. has the advantage that it is more powerful and therefore requires fewer patients than the classical Bonferroni correction in the case of two endpoints.

This testing procedure according to Roehmel et al. runs as follows:
First step
- In the first step a negative effect is ruled out for both endpoints. This assures that any positive effect in one endpoint (e.g. less pain measured by VAS) is not due a detrimental effect in the other endpoint (e.g. more rescue medication intake).

Second step
- Once the first step is successfully passed, overall superiority of Visanne over placebo can be tested in the second step using a global test on the combined endpoint VAS and rescue medication intake.

Third step
- When overall superiority of Visanne over placebo is proven, superiority of Visanne over placebo with regard to reduction of pain assessed by VAS can be tested without having to worry about possible confounding by rescue medication or multiplicity. Likewise, superiority with regard to rescue

medication intake can be tested without having to worry about possible confounding by VAS or multiplicity.

Results

Exposure
In study A32473, a total of 102 patients were included in the full analysis set (FAS) of the Visanne group compared to 96 patients in the placebo group. The mean treatment duration for Visanne-treated patients was 11.8 weeks and 11.9 weeks for placebo-treated patients.

Demographics
The demographic parameters age, height, body weight and BMI were comparable. The mean age of Visanne-treated patients was approximately 31 or 32 years. No relevant differences were found for the parameters height, weight, or BMI. The majority of patients were Caucasian and the study was conducted in Europe.

Efficacy results

EAPP measured by FAS

- **Pivotal placebo-controlled study A32473**

EAPP measured by VAS at 12 weeks of treatment compared to baseline was statistically significantly more reduced in the Visanne group as compared with placebo. The 3-step testing procedure showed that the effects of dienogest on EAPP were statistically significantly superior to those of placebo, in spite of the noticeable placebo effects. The significant effects of dienogest were evidenced as attributable to the decrease of VAS, as it was established that the decrease in intake of rescue medication was not significantly different under dienogest and under placebo.

Table 9: EAPP: absolute values (mean ± SD (mm)) and individual change by VAS (week 12- baseline), and 95% CI – Full Analysis Set (FAS)

	Visanne	Placebo		
VAS baseline	56.8 ± 18.0	57.0 ± 17.8		
VAS week 12	27.6 ± 20.4	39.4 ± 22.1		
Difference: week 12 – baseline*	-28.8 ± 24.5	-16.9 ± 16.0	Difference between means (placebo *minus* Visanne)	95% CI
Difference: week 12 – baseline, LOCF*	-27.4 ± 22.9	-15.1 ± 16.4	12.272**	6.403 to 18.140

* Negative difference reflects improvement.
** Positive value reflects difference in favor of Visanne.

50% and 75% responder rates in EAPP
Key secondary efficacy endpoints (i.e. 50% and 75% responder rates and VAS adjusted for rescue medication) were consistent with the primary efficacy results:

Reduction of endometriosis-associated pelvic pain by 50% or more without relevant increase of concomitant pain medication was achieved in 37.3% of patients on Visanne (placebo: 19.8%).
Difference: -17.5% (95%CI: -29.8 to -5.2; p=0.005).

Reduction of endometriosis-associated pelvic pain by 75% or more without relevant increase of concomitant pain medication was achieved in 18.6% of patients on Visanne (placebo: 7.3%).
Difference: -11.3% (95%CI: -20.5 to -2.2; p=0.015).

Efficacy on EAPP measured by VAS beyond 12 weeks of treatment: long-term (52 weeks) extension of study A32473 (A39700)
The double blind 12 weeks placebo-controlled study was followed by a 52-week extension in which all patients were treated with Visanne. Overall, 152 patients (90.5%) completed this study and only 1 patient (0.6%) discontinued due to lack of efficacy. A continuous improvement of mean VAS was observed, but due to the uncontrolled design and the unknown influence of rescue medication an assessment of long-term efficacy based on this extension study is problematic. Further, only those who benefit will continue, thus bias cannot be excluded. Therefore the only conclusion that can be drawn is that the results are not inconsistent with the results obtained in the double-blind period of this study. On the other hand, the underlying pharmacologic basis of reduction in pain, i.e. suppression of estrogen production is maintained, which is also shown in the long-term contraception studies performed with the combined oral contraceptive Qlaira.

- **Active controlled study (AU19)**

Multicenter, open-label, randomized, active controlled study to investigate the efficacy and safety of daily oral administration of 2 mg dienogest versus intramuscular administration of 3.75 mg leuprorelin acetate (LA) every 4 weeks in the treatment of pain associated with endometriosis over 24 weeks. As GnRH agonists are considered standard therapy in endometriosis treatment, the choice of the comparator LA is acceptable.

- **Primary efficacy variable VAS**

Change in the pelvic pain (VAS) after 24 weeks of treatment compared to baseline.
In general, there was a decrease in the VAS (i.e., a reduction of pelvic pain intensity) in both treatment groups over time. After 24 weeks of treatment, a mean decrease of the VAS of 47.5 mm was observed in the dienogest group and of 46.0 mm in the LA group (PP population).

Table 10: EAPP: absolute values and individual change (mean ± SD) by VAS (week 24- baseline) – FAS and PPS (study AU19)

	Visanne	LA
FAS		
VAS baseline	53.3 ± 29.1 mm (n = 118)	55.4 ± 24.2 mm (n = 127)
VAS week 24	12.1 ± 19.9 mm (n = 109)	13.0 ± 19.4 mm (n = 116)
Difference: week 24 – baseline*	-40.2 ± 32.0 mm (n = 108)	-41.8 ± 28.6 mm (n = 115)
PPS		
VAS baseline	60.2 ± 24.2 mm (n = 90)	57.9 ± 21.0 mm (n = 96)
VAS week 24	12.7 ± 20.3 mm (n = 90)	11.9 ±16.9 mm (n = 96)
Difference: week 24 – baseline*	-47.5 ± 28.8 mm (n = 90)	-46.0 ± 24.8 mm (n = 96)

* Negative difference reflects improvement.

In a previous national assessment of the RMS Study AU19 was rated as not being sufficient to demonstrate efficacy of Visanne in relieving endometriosis-associated pelvic pain (EAPP) because assay sensitivity of the non-inferiority design was considered not established in the absence of suitable placebo data. For the efficacy endpoint pelvic pain in endometriosis, a double-blind placebo-controlled study was requested. Therefore, the only conclusion that can be drawn is that the results on EAPP evaluated by VAS obtained in this study do not contradict those obtained in the pivotal placebo-controlled study.

Effects on endometrial lesions
Pre-GCP Studies A01177 and A01176

Studies A01177 and A01176 were conducted prior to implementation of GCP regulations. Nevertheless, they were conducted in accordance with all applicable national regulations valid at the time and according to best scientific practice.
Endometriotic lesions were assessed at baseline and end of treatment using the endoscopic endometriosis classification (EEC) according to Semm which was a commonly used scoring system at the time.

Table 11: Assessment of endometriotic lesions (EEC) after treatment in studies A01177 and A01176

Assessment of post-treatment endometriosis by EEC	Study A01177	Study A01176	
	Dienogest (2 x 1 mg) N = 100 (100.0%)*	Dienogest (2 x 1 mg) N = 97 (100.0%)*	NETA (2 x 5 mg) N = 48 (100.0%)
disappeared	65 (65.0%)	61 (62.9%)	30 (62.5%)
partially remitted	20 (20.0%)	25 (25.8%)	11 (22.9%)
unchanged	15 (15.0%)	11 (11.3%)	7 (14.6%)

* This number refers to the number of patients with post-treatment assessment. Some patients refused to have a post-treatment laparoscopy.

These results, though using a different rating scale of endometriotic lesions, showed a significant reduction in endometriotic lesions, which further support that dienogest addresses the underlying pathology of endometriosis.

Ongoing studies
There are no ongoing studies to investigate the efficacy or safety of Visanne in patients suffering from endometriosis.

However, further data are expected from an ongoing adult pharmacodynamic study 13180 which examines the influence of dienogest on several pharmacodynamic parameters at different dose levels and includes frequent assessment of hormone levels, see RMP.

In conclusion, the pivotal placebo-controlled study A32473 adequately demonstrated that Visanne was statistically significantly superior to placebo in the reduction of endometriosis related pain. Clinical relevance of this effect on VAS is supported by the substantial difference in 50% and 75% responder rates versus placebo. The placebo-controlled results of this study were supported by the results obtained in the active controlled study versus GnRH-agonist. Effects on endometriotic plaques were sufficiently evidenced by the results obtained in the dose-response study and both pre-GCP studies.

II.3.4 Clinical safety

Studies included in the clinical safety consist of nine clinical phase 2/3 studies. Six of these were the phase 2/3 studies presented in Clinical efficacy to demonstrate the efficacy of Visanne in the treatment of EAPP or in the reduction of endometriotic lesions using laparoscopic methods. Additionally, the safety data of three clinical phase 2/3 studies are included for completeness: study B567 was a phase 3 clinical study to compare the efficacy of dienogest (2 x 1 mg) with the GnRH analog triptorelin (Decapeptyl® 3.75) with regard to the recurrence of endometriosis in patients who had a surgical treatment of lesions before medication was started for 16 weeks. Study A04431 was a high-dose pilot (phase 2) clinical study to assess the efficacy of dienogest (2 x10 mg) on the laparoscopic classification of endometriosis after 24 weeks of treatment versus baseline. Study A05436 was a phase 2 clinical study to compare the efficacy of Visanne and LA in preparing the endometrium for ablation over a treatment period of 8 weeks.
The safety data from studies A32473, AU19, A39700 and A02266 are the most relevant to the safety assessment of Visanne and representative of the respective target population.

In total, 332 Visanne-treated patients_were assigned to the FAS of this safety assessment based on the pooled data of these studies. The following treatment groups are presented for comparison: placebo group with 96 patients (study A32473), LA group with 128 patients (study AU19) and 4 mg dienogest group with 34 patients (study A02266). The mean_treatment duration for patients on Visanne was 39.8 weeks (SD 19.0, range 0.1 − 68.0 weeks), for patients on placebo was 11.9 weeks (SD 1.9, range 0.6 − 6.0 weeks), for patients on LA was 23.6 weeks (SD 3.8, range 4.1 − 34.7 weeks); there is no information for the 4 mg dienogest group. In the one-year extension study A39700, 135 patients were treated with Visanne for at least 1 year.

General AE's and discontinuation
Based on the pooled analysis, a total of 296 (89.2%) of 332 patients completed treatment with Visanne, i.e. 36 patients discontinued treatment with Visanne. The most frequently reported reason for discontinuation of study medication in the Visanne group was AEs (4.5% based on the pooled analysis). Other reasons that led to discontinuation were reported for less than 3% of the population without any relevant differences between the studies or treatments.
Despite the observed degree of abnormal bleeding pattern, the rate of dropouts was low, which particularly holds for dropouts due to bleeding events. In addition, bleeding events were only occasionally reported as AEs, which might in part be attributable to the systematic assessment of bleeding data via daily diary, i.e. patients might not have felt the need to report specific events as AE in addition to filling in the diary.

Serious Adverse Events (SAEs) and deaths
In the 4 pooled studies (A32473, AU19, A39700 and A02266) a total of 15 SAEs occurred in 11 Visanne-treated patients, of which 5 were considered related to the use of Visanne. One SAE occurred in the LA treated patients, which was not related to the use of LA.(study AU19). The 5 SAEs related to the use of Visanne included depression,(3) and ovarian cysts (2).
None of the SAEs considered Visanne treatment-related gave rise to any safety concern, other than already known to occur during use of progestagen-only preparations.
No deaths were reported in any of the studies included in the development program of Visanne.

Adverse events
Overall, 768 AEs were reported by 205 (61.7%) of 332 women treated with Visanne. Placebo patients (26.0%) had fewer AEs compared to Visanne (33.3%). Both the higher dosage 4 mg dienogest group and the LA group tended to have more patients with AEs compared to Visanne (88.2% for 4 mg dienogest versus 79.3% for Visanne in study A02266; 76.6% for LA versus 70.8% for Visanne in study AU19).

In the Visanne group, the most frequently involved MedDRA primary SOCs were *Infections and infestations* (24.7%), *Nervous system disorders* (20.5%), and *Reproductive system and breast disorders* (18.7%). The most frequent MedDRA preferred terms were headache (17.8%), nasopharyngitis (7.2%) and nausea (6.6%) in this group.

Adverse Drug Reactions (ADRs)

A total of 386 ADRs were recorded for 119 (35.8%) of 332 women treated with Visanne. Placebo patients (7.3%) had fewer AEs compared to Visanne (14.7%) and the 4 mg dienogest and LA groups had the highest percentage of ADRs (88.2% for 4 mg dienogest versus 79.3% for Visanne in study A02266; 53.9% for LA versus 47.5% for Visanne in study AU19).
The most frequently reported undesirable effects under treatment with Visanne are headache (9.0%), breast discomfort (5.4%), depressed mood (5.1 %) and acne (5.1 %).
There were 24 ADRs categorized as common (≥ 1% up to < 10%): in order of decreasing frequency, these were headache, acne, nausea, increased weight, breast discomfort, depressed mood, flatulence, hot flush, uterine and vaginal bleeding (including spotting), ovarian cyst, asthenic conditions, loss of libido, nervousness, sleep disorder, abdominal pain, alopecia, irritability, altered mood, migraine, abdominal distension, vomiting and back pain.
All other ADRs were categorized as uncommon (≥ 0.1% up to < 1%).

- ***Bleeding events***

Bleeding events by MedDRA primary SOC were categorised as follows: dysfunctional uterine bleeding (1; 0.3%), metrorrhagia (1; 0.3%), menorrhagia (1; 0.3%), uterine hemorrhage (1; 0.3%), vaginal hemorrhage (1; 0.3%) as uterine/vaginal bleeding including spotting (5; 1.5%).

Irregular menstrual bleeding was assessed in studies A32473, A39700 and AU19 using daily diaries. In study A02266, bleeding patterns were documented in the case report form (CRF). Consequently bleeding events were only occasionally reported as AEs resulting in the above 5 cases classified as ADRs. This might give rise to underreporting of bleeding events, which are undesirable adverse events.
Therefore bleeding events are further assessed in detail in studies AU19, A32473 and A39700 using the WHO 90 days reference period method. In patients treated with Visanne, there was an increased incidence of prolonged bleeding (38%), irregular bleeding (35%) and infrequent bleeding (27%) at reference period 1 (first period of 90 days).
Later trends until completion of reference period 5 showed a strong decrease in prolonged bleeding (from 38% to 6%). Moreover, the incidence of frequent bleeding was substantially reduced at end of period 5 (from 13% to 0%). The incidence of irregular bleeding decreased consistently, notably from 35% in reference period 1 to 22% in period 4. By contrast, the proportion of patients with amenorrhea increased from 2% in period 1 to 28% in period 4. Despite the observed degree of abnormal bleeding pattern, the rate of dropouts due to bleeding problems was low; only 3 women (0.4%).

- ***Depression/depressive mood***

The most common psychiatric events were depression and depressive mood. It was difficult to assess the contribution of Visanne because it is known that endometriosis patients are at a higher risk for depression and depressive mood in comparison to the general population. The issue is addressed in the Risk Management Plan.

- ***Bone mineral density (BMD)***

BMD of the lumbar spine (L1-L4) was measured in a subgroup encompassing 64 patients by using DEXA (Studu AU19). In the Visanne group, the mean individual BMD percentage change (FAS population) was +0.25% ± 2.77 (mean ± SD) between screening and the final visit. The respective change in the LA group was -4.0% ± 4.84. The observed decrease in BMD in the LA group is in line with that reported in published studies that evaluated GnRH agonists in the treatment of endometriosis.
Further supportive data are expected from study 13180 which examines the influence of dienogest on several pharmacodynamic parameters at different dose levels and includes frequent assessment of hormone levels (see RMP).
However, at this moment data are limited. Therefore, the SPC contains a warning:
“In patients who are at an increased risk of osteoporosis a careful risk-benefit assessment should be performed before starting Visanne because endogenous oestrogen levels are moderately decreased during treatment with Visanne (see section 5.1).”
For section 5.1 of the SPC/PL the following wording is added: “Endogenous oestrogen levels are moderately suppressed during treatment with Visanne. Currently, long-term data on BMD and risk of fractures in users of Visanne are not available. BMD was assessed in 21 patients before and after 6 months of treatment and there was no reduction of mean BMD.”

Laboratory assessments
All haematology and blood chemistry parameters and liver enzyme parameters were within the normal ranges. Mean values for all lipid parameters (total cholesterol, triglyceride, HDL, LDL and very low-density lipoprotein [VLDL]) were within each respective normal post-baseline range, and stable throughout the entire treatment period in all treatment groups with comparable mean values across all treatments groups.
Hemostatic parameters were evaluated in the dose-finding study A02266. Mean values were stable during the 24 week treatment period for all hemostasis parameters analyzed in the 4 mg dienogest group. A comparison between treatments is not possible as measurements were made almost exclusively on patients taking 4 mg dienogest. Additional hemostatic parameters were assessed in study A04431 where a daily dose of 20 mg dienogest (10 times the dose of Visanne) was administered for 24 weeks. Even at this high dose, only mild changes of these parameters were observed.

II.3.5 Pharmacovigilance System and Risk Management System

Pharmacovigilance system
The Pharmacovigilance system as is 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 Plan
Visanne is a tablet containing 2 mg of dienogest. Dienogest initially has been developed as progestin compound for products used in the indications 'oral contraception' and 'menopause management'.
Dienogest in combination with ethinyl estradiol (EE) is marketed since 1995 in the indication 'oral contraception' under the trade name Valette®/Celimona® in some EU countries, among others Germany, but not in the Netherlands. A combination of estradiol valerate and dienogest is marketed since 2001 for continuous combined hormone replacement therapy (HRT) under the trade name Climodien® as well as in the indication Oral Contraception since 2009 under the tradename Qlaira®. Dienogest as sole active ingredient for the treatment of endometriosis is marketed in Japan since January 2008.

Visanne is targeted for the treatment of endometriosis.

Identified risks
Depression
Endometriosis and the associated chronic pelvic pain are probably associated with a higher prevalence of depression compared to women without chronic pelvic pain. From the clinical trials that have been conducted with dienogest there is no conclusive evidence that Visanne causes clinical depression. Depression caused by the chronic pelvic pain can be assumed to be improved during treatment with Visanne. In view of the presumed increased risk for depression in the target population and the two described case reports, the CCDS of Visanne will include the following warning in the section "Special warnings and precautions for use":
Patients who have a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.
In the section "Undesirable effects" *depressed mood, sleep disorder, nervousness, loss of libido*, and *mood altered* will be included as common undesirable effects of Visanne. *Anxiety, depression*, and *mood swings* will be included as uncommon undesirable effects.
During pharmacovigilance targeted monitoring activities all ADR reports with at least one MedDRA Preferred Term in the System Organ Class 'Psychiatric disorders' will be continuously evaluated on a monthly basis. In addition a specific follow-up questionnaire for serious case reports on psychiatric disorders will be used in order to adequately follow-up these cases.

BMD

GnRH analogues (e.g. LA) and high dose progestin only products (e.g. DMPA) lead to a decrease in the production of estradiol and a resultant decrease in BMD. However, at this moment data are limited. Therefore, the SPC contains a warning:
"In patients who are at an increased risk of osteoporosis a careful risk-benefit assessment should be performed before starting Visanne because endogenous oestrogen levels are moderately decreased during treatment with Visanne (see section 5.1)."
For section 5.1 of the SPC/PL the following wording is added: "Endogenous oestrogen levels are moderately suppressed during treatment with Visanne. Currently, long-term data on BMD and risk of fractures in users of Visanne are not available. BMD was assessed in 21 patients before and after 6 months of treatment with Visanne and there was no reduction of mean BMD. In 29 patients treated with leuprorelin acetate (LA), a mean reduction of 4.04% ± 4.84 was noted after the same period (Δ between groups = 4.29%; 95%CI: 1.93 – 6.66; p<0.0003).".

Missing information
Pediatric use
Based on the experience with other progestin-only preparations (e.g. Microlut, Noristerat, Primolut) there is no evidence of a different ADR profile in adolescents when compared to adults. There is no evidence of a special susceptibility to ADRs in adolescents. There is currently no experience in adolescents treated with Visanne in the indication endometriosis.

Spontaneously reported suspected adverse drug reactions remain the most important source of detecting safety issues in the post-authorization phase. During pharmacovigilance targeted monitoring activities all ADR reports that occur in patients younger that 18 years of age will be continuously evaluated on a monthly basis. In addition, a specific follow-up questionnaire for case reports on patients younger than 18 years will be used in order to adequately follow-up all suspected ADRs in adolescents.
The MAH will conduct a multinational post-marketing observational study in users of Visanne (*Vis*anne *P*ost-Marketing *O*bservational *S*tudy/VIPOS). This non-interventional study will be aimed to collect data on the improvement of symptoms of endometriosis and data on the safety of Visanne during typical use of Visanne with a special focus on adolescents. The observational period will be one year.

Important potential risks
The following further important potential risks are discussed for progestin-only preparations in the scientific literature and are addressed in the current version of the CCDS for Visanne:
- Cardiovascular events
- Cerebrovascular events
- Ectopic pregnancy
- Breast cancer
- Benign and malignant liver tumors
- Recurrence of cholestatic jaundice
- VTE and ATE

Pharmacovigilance Plan
To the opinion of the MAH, except for routine pharmacovigilance practices, no further action with regard to these topics is deemed necessary. No risk minimization activities are deemed necessary. This is deemed acceptable.

Periodic Safety Update Report (PSUR)
The MAH will submit PSURs according to the following scheme:

- After Day 210 after authorisation at least every 6 months
- After initial placing on the EU market:
    - 6-monthly PSUR submissions should be continued until two full years of marketing experience in the EU has been gained.
    - thereafter yearly PSURs for the following two years; and
    - thereafter PSURs should be submitted at 3-yearly intervals.

The MAH will inform as soon as possible the RMS and CMSs of the date of granting of the first marketing authorisation in the EU.

Product information

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 test was performed in two phases with 10 participants each. The test persons are women aged 15 to 55 years with a mean of 37.7 years. 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 PL. 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.

Participants were interviewed individually by one experienced and trained interviewer. Another interviewer observed the behaviour of the participant. Each interview was digitally recorded and the responses were written down by hand. Respondents were asked to give their answer in their own words.

A satisfactory outcome was achieved when 16 out of 20 participants were able to find information and answer each question correctly and act appropriately.

The results of the test were satisfactory. In the first round information for all 14 questions was found and a correct explanation provided by at least 9 of 10 participants. Therefore no further changes were considered to be required. In the second round all subjects located and correctly explained the information for all 14 questions. One question generated a low average ease score as 5 subjects took longer to respond. Since there appeared to be no barrier to these subjects' understanding of the requested information, no further action was deemed necessary. This is acceptable. The readability test has been sufficiently performed.

III BENEFIT-RISK ASSESSMENT

The MAH proposed a revised indication "treatment of endometriosis" for the synthetic progestagen dienogest in a dose of 2 mg/day taken continuously, the initial applied indication was long-term treatment of endometriosis in women from menarche to menopause .

Progestagen monotherapy is an established treatment in endometriosis; several progestagens, i.e. medroxyprogesterone, norethisterone, dydrogesterone, lynestrenol, are approved in the Netherlands and other EU countries for more than 30 years for the indication of treatment of endometriosis. According to a recent review by Vercellini et al. 2003 and the most recent Cochrane Review on this topic continuous progestagens appear effective therapies for the treatment of painful symptoms associated with endometriosis (Prentice et al. 2000).

Benefit

Reduction in EAPP

With the pivotal efficacy study A32473, a multicenter, double-blind, randomized, placebo-controlled, parallel-group trial designed to prove superiority of Visanne in the treatment of EAPP in comparison to placebo it is adequately demonstrated that Visanne was statistically significantly superior to placebo in the reduction of endometriosis related pain. Within this study, the MAH has taken efforts to ascertain that the noted positive effect in one endpoint (e.g. less pain measured by VAS) is not due to a detrimental effect in the other endpoint (e.g. more rescue medication intake). The currently presented analyses have adequately shown that this is not the case. Retrospectively, it is noted that when the company had corrected for multiple comparisons by the Bonferroni method, these results would not have changed.

Clinical relevance of this effect on VAS is supported by the substantial difference in 50% and 75% responder rates versus placebo. These results were further strengthened by calculations of differences in 50% and 75% responder rates and VAS adjusted for rescue medication, at week 12 between Visanne and placebo with corresponding 95% CI and p-values showing the differences to be statistically significant.

Long-term efficacy on EAPP measured by VAS is not established in a double-blind manner, but for a considerable long time period, i.e. 52 weeks open extension of the 12-week placebo-controlled study. Further, the majority of women entered the open uncontrolled phase and only few discontinued due to lack of efficacy. However, decisive is considered the mode of action; dienogest has proven progestagenic action, and in this dose the suppression of estradiol production is such that ovulatory inhibition is achieved. As the underlying pharmocological basis, i.e. suppression of estradiol levels, remained constant over more than one year treatment it is unlikely that efficacy in reduction of EAPP will diminish over time.
Sustained suppression is previously shown with dienogest in this dose leading to ovulatory inhibition in the long-term contraception studies performed with the combined oral contraceptive Qlaira. As in the revised indication wording 'chronic' has now been deleted from the indication, the current uncontrolled long-term efficacy data are considered sufficient.

The efficacy of Visanne in EAPP in comparison to the standard therapy of a GnRH agonist is difficult to assess. The one active controlled trial versus LA was considered insufficient to assess non-inferiority against LA in the absence of a placebo-arm. Further, public literature on GnRH-agonist or progestagen treatment for endometriosis related pain rated by VAS is sparse; only a few small studies are available. This was reflected by the very limited number of historical data on GnRH-agonist studies that evaluated pelvic pain that were used to support the non-inferiority margin of this trial.

Reduction in endometrial plaques

The demonstrated substantial reduction in endometriotic lesions established by laparoscopy in the 24-week dose-response study and the 2 pre-GCP 24-week studies are considered sufficient proof of the pharmacological effect of dienogest 2 mg dose on endometriotic lesions.

In conclusion, the pivotal placebo-controlled study A32473 adequately demonstrated that Visanne was statistically significantly superior to placebo in the reduction of endometriosis related pain. Clinical

relevance of this effect on VAS is supported by the substantial difference in 50% and 75% responder rates versus placebo.
The choice of the new clinical endpoint of EAPP is endorsed as, from a clinical point of view, pelvic pain is the most relevant symptom of endometriosis.
The pharmacological basis of the significant reduction in endometriosis-related pain is sufficiently substantiated by the noted substantial reduction in endometriotic lesions established by laparoscopy.
Though the long-term efficacy data were uncontrolled in design, it is unlikely that, considering the underlying pharmacologic basis i.e. suppression of estrogen production, the reduction in pain will diminish over time.
In conclusion, currently submitted evidence sufficiently demonstrated the efficacy of dienogest in the indication treatment of endometriosis.

Risk
Clinical safety of dienogest 2 mg was adequately documented; 332 Visanne-treated patients were in the pooled safety data base of Visanne. The number of patients treated for at least 1 year is considered sufficient. The most frequently reported undesirable effects are headache, breast discomfort, depressed mood and acne. As irregular bleeding was assessed by using daily diaries, bleeding events were only occasionally reported as AEs, and only 5 cases classified as ADRs. Thus, this approach might give rise to underreporting of bleeding events, which are undesirable adverse events. However, actually, as with other progestagen-only therapies the main problem with Visanne is irregular, prolonged or more frequent bleeding. Assessment of the daily bleeding diaries indicated the frequency of irregular bleeding as high as 35% during the first 90 days of treatment. However, frequencies decreased considerably over time. Despite these high percentages, the number of women who discontinued due to bleeding problems was low, only 3 women (0.4%).
By contrast, the proportion of patients with amenorrhea increased from 2% in period 1 to 28% in period 4. Effects on BMD, measured in the active controlled study versus LA over a period of 24 weeks by DEXA in a limited number of patients, indicated that effects of Visanne on BMD are virtually absent, while with LA a marked decrease in BMD was noted of -4.0%.
In conclusion, the safety profile of Visanne is considered acceptable and considered favourable in comparison to GnRH-agonists which introduce a temporary postmenopausal state with high frequency of hot flushes and decrease in BMD. The latter negative effect on BMD limits GnRH-treatment to 6 months.

Benefit-risk balance
The efficacy of Visanne in the treatment of endometriosis related pain is considered adequately established versus placebo, although long-term efficacy was evaluated in an uncontrolled design. However, as the pharmocological effect, i.e. suppression of estradiol levels remained constant over more than one year treatment it is unlikely that efficacy in reduction of EAPP will diminish over time.
The pharmacological basis of the significant reduction in endometriosis-related pain is sufficiently substantiated by the noted substantial reduction in endometriotic lesions established by laparoscopy.
Whether the degree of efficacy in EAPP is also achieved with other treatments approved in the indication of endometriosis, is difficult to assess as published data are still limited.
The safety profile, dominated by an initial high number of women reporting bleeding irregularities, is clearly favourable to that of the standard therapy of GnRH agonists as no adverse effects on BMD are noted and vasomotor symptoms like hot flushes are substantially less. In conclusion, the benefit risk balance of Visanne is considered positive.

IV OVERALL CONCLUSION

The first assessment report of the MEB was discussed in the Board meeting of 26 February 2009. The Board decided to follow the advice of the assessors, but an additional question was raised on the assay sensitivity of the only one pivotal placebo-controlled trial. This question was also raised because the results obtained in the active controlled non-inferiority study versus LA in the new endpoint of endometriosis associated pelvic pain (EAPP) are considered only supportive. Therefore, further argumentation was needed why the submitted evidence is sufficient to assess the benefit/risk for the indication of endometriosis in view of this one new placebo controlled study with EAPP as endpoint. The

wording of the indication was thoroughly discussed as more dimensions of endometriosis can be considered (pain, Quality of life, proliferation of endometriosis). It was added as question to the applicant, that the proposed indication ('long-term treatment of endometriosis in women from menarche to menopause') does not reflect the primary efficacy data, i.e. efficacy of Visanne in endometriosis related pain.
The questions from the RMS were supported by the Concerned Member States, but an additional question on the long-term treatment was added, because data on endometriosis associated pelvic pain (EAPP) are limited in terms of duration even if Study A32473 was followed by a 52-week open label follow-up study.

The second assessment report of the MEB was discussed in the Board meeting of 27 August 2009. The Board supported the view of the assessors that there is no objection against the choice of EAPP instead of a laparoscopic evaluation of the endometriotic plaques at study completion. Taking the additional background information into account, the Board considered the current data present in the registration file as sufficient to grant the revised indication of "Treatment of endometriosis".
This view was shared by the Concerned Member States. During the Decentralised Procedure a number of other 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.

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 2 December 2009.

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. Visanne tablets from Bayer BV was authorised in the Netherlands on 21 December 2009.

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.

Area	Description
Quality	The forced degradation study will be performed in order to prove the stability indicating nature of the HPLC method for the assay and related substances determination. The relevant data will be provided post-approval by end of February 2010.
Quality	A test on water content will be included in follow-up stability studies (at least one batch per year is stored at 25°C/60% RH and tested yearly). A limit for water content will be included in the shelf life specifications if an increase or decrease in water content is observed.

Non-Clinical	An updated ERA will be submitted in February 2010.
Cinical	The full study protocol for the Visanne Post-Marketing Observational Study (VIPOS) study is expected within 6 months after approval
Clinical	The final study protocol on the paediatric study will be submitted as soon as available

List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
ASA	Active Systemic Anaphylactic
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
ATE	Arterial thromboembolism
AUC	Area Under the Curve
BMD	Bone mineral density
BP	British Pharmacopoeia
CBG	corticoid binding globulin
CCDS	Company Core Datasheet
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
CMS	Concerned Member State
CV	Coefficient of Variation
E2	Estradiol
EAPP	Endometriosis-associated pelvic pain
ECG	Electrocardiograph
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEC	Endoscopic endometriosis classification
EU	European Union
FAS	Full analysis set
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GnRH	Gonadotropin-releasing hormone
GPT	glutamic pyruvic transaminase
GSH	glutathione
GST	glutathione-S-transferase
HDL	High-density lipoprotein
HRT	Hormone replacement therapy
ICH	International Conference of Harmonisation
LA	Leuprorelin acetate
LDL	Low-density lipoprotein
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
MedDRA	Medical Dictionary for Regulatory Activities
NETA	Norethisterone acetate
NfG	Note for Guidance
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
PCA	Passive Cutaneous Anaphylaxis
PDCO	Paediatric Committee
Ph.Eur.	European Pharmacopoeia
PIP	Paediatric investigation plan
PL	Package Leaflet
PSUR	Periodic Safety Update Report
rAFS	score for reduction of endometric lesions assessed by laparoscopy

RMP	Risk Management Plan
RMS	Reference Member State
SAE	Serious Adverse Event
SHBG	sex hormone binding globulin
SD	Standard Deviation
SOC	System organ class
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
UDS	Unscheduled DNA Synthesis
USP	Pharmacopoeia in the United States
VAS	Visual Analog Scale
VLDL	Very low-density cholesterol
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