Australian Government

Department of Health and Ageing

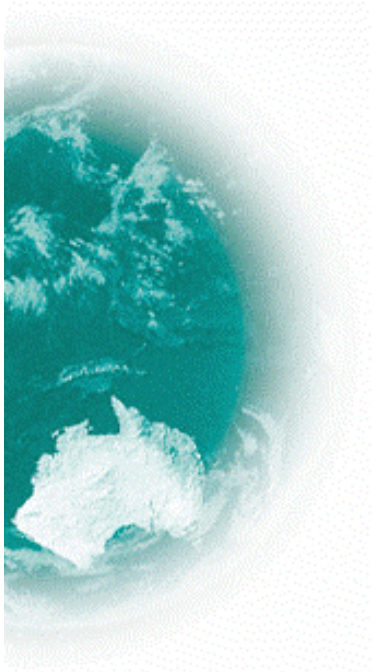
Therapeutic Goods Administration

Australian Public Assessment Report for Dienogest

Proprietary Product Name: Visanne

Submission No: PM-2009-00539-3-5

Sponsor: Bayer Australia Ltd



September 2010

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I. Introduction to Product Submission

Submission Details

Type of Submission	Extension of indication
Decision:	Approved
Date of Decision:	25 May 2010
Active ingredient(s):	Dienogest
Product Name(s):	Visanne
Sponsor's Name and Address:	Bayer Australia Limited 875 Pacific Highway, Pymble, NSW 2073
Dose form(s):	Tablet
Strength(s):	2 mg
Container(s):	Polyvinyl chloride (PVC)/aluminium (Al) blister strips /cardboard carton with 2, 6 or 12 blister strips.
Pack size(s):	Each blister strip has 14 tablets.
Approved Therapeutic use:	For the treatment of endometriosis.
Route(s) of administration:	Oral
Dosage:	The proposed dose is one 2 mg tablet every day, with no break in treatment.
ARTG number(s):	160465

Product Background[1]

Endometriosis is a gynaecological disease characterised by the presence of endometrial tissue outside the uterine cavity. These deposits are usually found within the pelvis (for example, ovaries, peritoneum and so on) but can rarely occur at extra-pelvic sites[i]. The most widely held theory regarding the aetiology of endometriosis involves retrograde reflux of menstrual tissue from the Fallopian tubes during menstruation, although it is being increasingly recognised that immune system factors are involved with disease development and progression[ii]. Endometriosis becomes apparent in the reproductive years when the lesions are stimulated by hormones. The characteristic clinical features include dysmenorrhoea, pelvic pain, which is often cyclical, and dyspareunia, with infertility or subfertility often associated with endometriosis[i].

Estimates of the frequency of endometriosis are variable, with the best estimate of prevalence being around 10%[iii,iv]. There are no sufficiently sensitive and specific signs and symptoms or non-invasive tests for the diagnosis of endometriosis, and visual inspection of the pelvis at laparoscopy, complemented by histological evaluation is still considered the "gold standard" for diagnosis[i,v].

The fact that invasive diagnostic procedures are required may well be the reason for significant delays in the diagnosis being made in symptomatic women[vi]. Due to this delay in diagnosis, chronic nature of the disease, and its prevalence in an economically active population, endometriosis has been found to place a substantial economic burden on society[vii].

In patients with severe endometriosis, or patients wishing to become pregnant in the near future, laparoscopic ablation of visible endometriotic lesions is considered the preferred treatment option[v].

[1] For references quoted in this sections, see Appendix 1.

As endometriosis is a hormone dependent disease, with ectopic endometrial implants being dependent on ovarian steroid hormones[viii], medical treatment with hormone manipulation is often used in mild to moderate cases. The establishment of a steady hormonal environment and inhibition of ovulation can temporarily suppress ectopic implants and reduce inflammation as well as associated pain symptoms[ix].

Currently employed medical therapies include danazol, gonadotrophin-releasing hormone (GnRH) analogues, and progestins. Also, despite not being licensed for this indication, combined oestrogen/progesterone oral contraceptives have been used with good effect by gynaecologists[ix]. However, a review of the limited data with combined oral contraceptives found no evidence of any difference in reduction of endometriosis associated pelvic pain (EAPP) but commented that there was a distinct lack of studies investigating this[x].

Suppression of endogenous oestrogen production (high dose progestins, GnRH analogues) leads to a hypo-oestrogenic state, which has been demonstrated to be effective in reduction of EAPP and causing atrophy of the lesions[ix]. Androgens such as danazol induce amenorrhoea through suppression of the hypothalamic-pituitary-ovarian axis accompanied by an increase in serum androgen levels and reduction in circulating oestrogen[xi]. There appear to be few differences in the effectiveness of the different medical treatment strategies in treating EAPP[ii]. Danazol and GnRH have proven efficacy and other drugs have been compared to these in randomised comparisons, and have appeared no better or worse, so by extrapolation it is concluded that they are also effective treatments[ii]. The major difference between these treatments is their differing adverse effect profiles, and the ability of patients to tolerate these[ii]. Adverse effects associated with the induced hypo-oestrogenic state (such as hot flushes and reduced bone mineral density (BMD) and androgenic effects (for example, acne, alteration in lipid profile, hirsuitism) have been considered limiting factors, especially when considering long term therapy[v]. Also, it seems that there is still dissatisfaction amongst patients regarding the effectiveness of therapies in managing their symptoms, and the impact the condition has on their lives, which is prompting ongoing work in to developing new treatment strategies[xii,xiii].

Dienogest (DNG) is a derivative of 19-nortestosterone which is reported to display no androgenic properties, and despite binding to progesterone receptors with only 10% of the affinity of progesterone, there are reports of good progestogenic effects on the uterus. It is considered to have low impact on hepatic and bone metabolism. Due to its activity, and potentially favourable side effect profile, it has been submitted for evaluation as monotherapy for the treatment of endometriosis.

Regulatory Status

There are no registered tablets containing dienogest alone in Australia. Dienogest is currently already available in Australia as a fixed combination product with ethinyl oestradiol (Valette), licensed for use in contraception and treatment of acne in women desiring contraception. It was approved by the TGA in 2007. This fixed combination product is also available in several European countries, along with another combination product Climodien which contains dienogest in combination with oestradiol valerate and is licensed for hormone replacement therapy.

Visanne was submitted to the European Union (EU) for evaluation on 27th November 2008. It was planned to submit an application for registration in Canada in the 3rd quarter of 2009. There are no current plans to register Visanne in the USA.

An application for the use of dienogest 2mg for the treatment of endometriosis was previously submitted to the Medicines Evaluation Board (MEB) in The Netherlands in 2001. Following a deficiency letter from the MEB, the application was withdrawn in 2003 due to the absence of a double-blind, placebo controlled, phase III study. Subsequently, Bayer commenced the placebo-

controlled trial (A32473) in 2004, with ongoing consultation with the MEB regarding data sample size, data collection and statistical analysis.

In Japan, a product called Dinagest (manufactured by Mochida Pharmaceutical Co.), which contains 1mg dienogest, has been marketed since January 2008 in a dose of one tablet twice daily for the treatment of endometriosis.

Product Information

The approved Product information (PI) document current at the time this AusPAR was prepared is at Attachment 1.

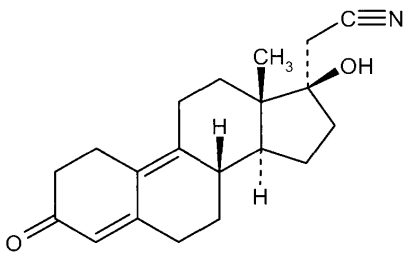
II. Quality Findings

Given that this product is a simplification of registered products (monotherapy compared to fixed-dose combinations), no significant issues were encountered during the evaluation; appropriate bioavailability data were provided and the formulation proposed for supply in Australia is the same as the formulation used in the Phase III efficacy studies.

Drug Substance

Dienogest is an anti-androgenic agent that acts on endometriosis by the endogenous production of oestradiol. It is not naturally occurring and purely synthetic (see structure below). Identification of dienogest is confirmed by 2 independent procedures and spectral comparison. This is acceptable.

Figure 1. Chemical structure.



$C_{20}\ H_{25}\ N\ O_2$ 311.43

Drug Product

Dienogest is manufactured and controlled (including appropriate limits for particle size distribution) as for the currently registered products. The drug product is well controlled with satisfactory limits for assay and dissolution rate. There are no specified degradants and the expiry limits are acceptable for any individual degradants and for total degradants. These limits are within ICH guidance limits for this maximum daily dose.

Stability data was provided to support the proposed shelf life of 5 years when stored below 25ºC in PVC/Al blister packs. Light had an effect on the assay of the tablets when they were stored in the open, but not when they were stored in the proposed green blister pack and the carton labels include the statement '*Do not remove from primary pack except for immediate use*'.
The product was developed to ensure optimum performance in relation to dissolution rate and other tablet characteristics including, but not limited to, hardness, content uniformity and disintegration. The excipients had already been used in combination tablets containing dienogest and ethinyloestradiol (Valette).

There were 3 validation batches of the current formulation. These batches confirmed that the current requirements for potency, content uniformity, related substances and dissolution rate were met.

Bioavailability

The formulation used in the Phase III efficacy studies was the same as proposed for supply in Australia (there has been a change in appearance, but this was justified with comparative dissolution data).
Two bioavailability studies were provided. The dienogest levels in the subjects' serum samples were determined using appropriately validation radioimmunoassay (RIA) methods.

Study B501 determined the absolute bioavailability of a 2 mg tablet[2] against a 2 mg intravenous (IV) dose (see also Section *IV. Clinical Findings, Bioavailability Studies* below)[3]. The study design and test method used were acceptable and it was concluded that the absolute bioavailability (area under the concentration–time curve, AUC) of dienogest from the 2 mg tablet was 90.6% (90% confidence interval (CI) was 86.6-94.7%).

Study BO08 investigated the relative bioavailability of the proposed 2 mg tablet formulation with and without food (high fat meal). The study design and test method used were acceptable and it was concluded that food had no effect on the bioavailability (90% CI for AUC was 95.1-103.9% and that for maximum plasma concentration (C_{max}) was 85.5-104.4%). See also section *IV. Clinical Findings, Bioavailability Studies* below.

Quality Summary and Conclusions

There are no objections to the registration of these products with respect to pharmaceutical chemistry and quality control.

With respect to bioavailability: the absolute bioavailability is ~91%; and food has no effect on the bioavailability.

III. Nonclinical Findings

Introduction

The sponsor submitted all of the available nonclinical data for dienogest. Most of this information had been previously submitted to the TGA. Of relevance to the extension of indication were one new *in vivo* pharmacology study and a number of studies published in the literature.

Pharmacology

Dienogest was shown to decrease the proliferation of cultured endometrial cells from rats and humans *in vitro*. In two models of angiogenesis (the mouse dorsal air sac assay and chick embryo chorioallantoic membranes), dienogest displayed inhibitory activity.

Two separate studies examined the effects of dienogest in an experimental model of endometriosis in rats. In the first, a Japanese study reported in the literature, dienogest had a clear effect: reducing the volume of endometrial implants in a renal subcapsular site, with 0.1, 0.3 and 1 mg/kg/day orally (PO) doses all having about the same effect (~50% reduction), and 0.03 mg/kg/day having a smaller effect. Dienogest had no effect on uterine weight, but decreased the number of peritoneal fluid cells and splenic cells, increased the natural killer cell activity of these cells and decreased the interleukin (IL)-1β production by peritoneal macrophages.

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[2] This was not the proposed formulation but dienogest in this product is BCS Class 1 and the results can be considered relevant to the proposed formulation. The Biopharmaceutics Classification System (BCS) is a guidance for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. According to the BCS, drug substances are classified as follows: Class I: high permeability, high solubility; Class II: high permeability, low solubility; Class III: low permeability, high solubility; Class IV: low permeability, low solubility.

[3] 2 mg of dienogest was provided dissolved in 2.5 mL of ethanol and this was further diluted in 50 mL of normal saline.

In the sponsor's own study, the response of the endometrial implants to dienogest in the rat was dependent on the location of the endometrial implant. In the mesenterial location, dienogest and danazol had very little effect on the endometrial implant, whereas in the peritoneal location 0.3 mg/kg/day dienogest PO significantly decreased the size of the endometrial implants (by ~30%), with no effect on uterine weight. However, unlike the Japanese study, a higher dose of dienogest (1 mg/kg/day) resulted in larger endometrial implants than controls and heavier uteruses. The study authors suggested that this might have been because of oestrogenic effects of dienogest, which have been reported previously.

Differing effects for differing doses of dienogest were also observed in a study conducted in the 1970s, in which the effect of dienogest on traumatised uterine endometrium in rats was investigated. A dose of 8 mg/animal/day dienogest resulted in 4/17 rats having deciduoma reactions at the traumatised sites, whereas none of the low dose (1 mg/animal/day) or high dose (64 mg/animal/day) had deciduoma reactions. As a comparison, between 88% and 100% of the rats treated with levonorgestrel or progesterone had deciduoma reactions.

Thus, the nonclinical evidence indicates that dienogest can inhibit endometrial proliferation and angiogenesis, both of which are important in endometriosis. The rat model of endometriosis provided inconsistent evidence of efficacy, with the Japanese group finding that dienogest was effective at many doses, whereas in the sponsor's study, dienogest was only effective in a narrow dose range. Dienogest was also shown to be partially effective in a narrow dose range in rats with a traumatised uterine horn. In conclusion, the nonclinical data are consistent with efficacy in the treatment of endometriosis, although the sensitivity of efficacy to dienogest dose is unknown.

Pharmacokinetics

No nonclinical pharmacokinetic studies were submitted.

Toxicology

This is the first product in which dienogest will be the only active ingredient. However, most of the nonclinical toxicity studies conducted with dienogest to support the registration of the existing combination products were conducted with dienogest alone, not in combination with an oestrogenic compound. The proposed dose of dienogest (2 mg/day) is the same as that registered for most of the dienogest-containing products (Valette, Climodien, Climodien 1/2 and some of the Qlaira tablets), and less than that provided by the highest strength Qlaira tablets (3 mg/day). The existing nonclinical toxicity studies are therefore considered adequate for the registration of Visanne. No new safety issues are expected to occur for this product with this new indication. Progestin-only tablets containing other progestogens have been registered for a considerable period of time, including for the treatment of endometriosis. Thus the absence of oestradiol from the tablet is not expected to result in unexpected toxicities.

Nonclinical Summary and Conclusions

- Adequate nonclinical data were submitted to support this application.
- The nonclinical data are consistent with efficacy in the treatment of endometriosis.
- No new nonclinical safety issues are raised by the application.
- There are no nonclinical objections to this new formulation and extension of indication.

IV. Clinical Findings

Introduction

The application to register Visanne in Australia consisted of complete study data from 29 trials. There were 20 clinical pharmacology studies submitted for evaluation. The majority of the studies are reported to have been carried out according to Good Clinical Practices (GCP) guidelines. However, as the pharmacology of dienogest (DNG) has been studied for many years, some of the studies were conducted in the pre-GCP era, and this is mentioned for the individual studies as they are summarised in this report.

Efficacy data were generated from a total of six clinical trials with 677 patients being treated with dienogest ≥2mg daily. Two separate primary endpoint parameters have been used in these studies to demonstrate efficacy in the "treatment of endometriosis". Historically, a common parameter used to investigate the effectiveness of treatments for endometriosis has been resolution of lesions seen at laparoscopy or laparotomy. Data from three phase 2/3 studies (A02266, A01177 and A01176) were submitted for evaluation to demonstrate the efficacy of Visanne in reduction of endometriotic lesions. Lesions and grading of endometriosis in the later studies was recorded by revised American Fertility Society (rAFS)[xiv]/ revised American Society for Reproductive Medicine (rASRM)[xv] classification scores. Earlier studies used the Endoscopic Endometriosis Classification (EEC) classification system which was widely used in Germany before the rAFS became standardised globally. This earlier classification has been subsequently correlated with the rAFS score[xvi]. However, reduction in volume of endometriotic lesions has been shown to correlate poorly with symptoms experienced by patients[xvii].

Furthermore, the main clinical problem caused by endometriosis is pelvic pain[xvii], and the focus of medical treatment should be on symptom relief[ix,xi]. Therefore, later research efforts into treatment of endometriosis have been increasingly based on reduction of symptoms.

Data from three phase 3 studies (the pivotal studies A32473 and AU19, together with the extension study A39700) were submitted for evaluation to demonstrate the efficacy of Visanne in reducing endometriosis associated pelvic pain (EAPP) and symptoms. Reduction in pain was quantitatively assessed by means of the Visual Analogue Scale (VAS). This is widely used to assess pain in many conditions, both acute and chronic, and its validity and reliability have been demonstrated[xviii]. However there does seem to be some controversy surrounding the minimal clinically important difference (MCID), and it seems to vary for different conditions. Initial studies of acute pain described the MCID as the difference in millimetres between VAS scores when pain was reported as a "little more" or a "little less", and has been reported from 13 to 16mm[xix,xx,xxi]. Other studies have put the MCID as high as 35mm[xviii,xxii], but this involves description of "adequate pain control" as opposed to perceptible improvement in pain. It also seems as though the MCID values are lower for chronic compared to acute pain[xviii].

Other effects of symptoms have been studied as secondary outcome measures during development of Visanne, such as physical findings as assessed by the Biberoglu and Behrman (B&B) rating scale which was specifically devised to assess the symptoms and signs of endometriosis[xxiii]. Whilst it has never been formally validated, its use has been widespread in studies on endometriosis. The SF-36™ Health Survey questionnaire is a validated and globally accepted standard for quality of life which is applicable to different conditions.

Safety data were supplied with all six efficacy studies, and three other studies were included for completeness (B567, A04431 and A05436). These three other studies utilised different doses of DNG or different dosage regimens or different study populations, and thus do not match the marketing application for Visanne, but do provide more data regarding the safety of exposure to DNG, so have been evaluated in this report.

Pharmacokinetics

The clinical pharmacology of DNG has been studied over the past decades, and as such some of the studies included in the submission were concluded prior to the implementation of GCP (B475, B476, and B478).

The bioanalysis of DNG in serum was performed in most studies for developing Visanne using radioimmunoassay (RIA). Study A00681 performed in Japan used high performance liquid chromatography (HPLC). Earlier studies used liquid scintillation counting (LSC) of radio-labelled DNG after extraction (as no specific RIA for DNG had been developed at that time).

The RIA used a highly specific antibody with no notable cross-reactivity with endogenous steroid hormones, and fulfilled the criteria for sensitivity, specificity, accuracy and precision. The LLOQ ranged between 0.2 – 1.0 ng/mL. The RIA was also subsequently cross validated with HPLC and mass spectrometry, with good agreement.

Physicochemical Characteristics and Formulations Used

In the first phase I studies of the development of Visanne, an initial gelatin-containing tablet formulation was used. The tablet core contained gelatin as a binder with lactose and potato starch as fillers. As a result of concerns regarding gelatin and the use of potentially transmissible spongiform encephalopathy transmitting agents, together with gelatin being seen as critical to dissolution behaviour over time, gelatin was replaced in the final tablet formulation by povidone. Also the fillers were modified by increasing the amount of lactose and potato starch and replacing some of the lactose with microcrystalline cellulose.

The final tablet formulation was used in most of the key studies, that is, two of the three key Pharmacokinetics (PK) and bioavailability studies (B276 and BO08), and two of the pivotal phase III clinical trails (A32473 and AU19). It was also used in the one year extension of one of the pivotal clinical studies (A39700) and QT interval prolongation (of the cardiac repolarisation as measured by electrocardiogram, ECG) study (A35653).

The initial gelatin containing formulation was used in the other study on the absolute bioavailability of DNG (B501). Similar gelatin containing formulations were used in the dose finding clinical study (A02266).

In vitro dissolution profiles of both the initial and final tablets fulfilled release specification and thus the formulations were considered similar, and the PK and PD data obtained representative of the final formulation.

Bioavailability Studies

Study B501 was performed to determine the absolute bioavailability of DNG. It was a single centre randomised crossover study in 22 healthy young males aged 22-31 years. Although Visanne is intended for use in women, the relative oral bioavailability and effects of food (BO08) and the absolute bioavailability (B501) were studied in men. This was done for logistical reasons and in men there is no need to synchronise dosing with menstrual cycle or to wash-out preceding hormonal medication. This is justified in the submission because the studies investigate formulation effects by intra-individual comparison, so selected study population should not affect validity. The two treatments were a film coated gelatin-containing tablet, and an aqueous alcoholic solution for intravenous (IV) injection, both containing 2mg DNG. There was a washout period between them of 7 to 14 days. Blood samples were collected at regular intervals until 48 hours post dosing and DNG sampling was performed by RIA with a Lower limit of quantitation (LLOQ) of 1.0ng/mL. The mean pharmacokinetic parameters are summarised in Table 1. The absolute bioavailability of the tablet was 90.6% (90%-Confidence Interval (CI): 86.6 – 94.7). Some aspects of this study are also described in Section II *Quality Findings.*

Table 1.

TT 7: **Mean PK parameters of DNG obtained in healthy young men after single oral and intravenous administration of 2 mg DNG**

Study report B501 (5.3.1.1 B501)

Parameter	Unit	2 mg DNG film-coated tablet (N = 20)			2 mg DNG i.v. (N = 20)		
		Arith. mean	CV%	Geom. mean	Arith. mean	CV%	Geom. mean
C_{max}	ng/mL	40.0	18.7	39.4	111	36.4	104
t_{max}	h	1.5 (0.5 – 4.0) (median and range)			N/A	N/A	N/A
$t_{1/2}$	h	8.48	14.4	8.37 (median)	8.64	13.6	8.20 (median)
AUC(0-48h)	ng·h/mL	428	19.9	420	472	17.9	465
AUC	ng·h/mL	456	18.6	448	501	16.7	495

Study BO08 had two objectives, the first being to determine the relative bioavailability of DNG from a final tablet form compared to micro-crystalline suspension after fasting. The second objective was to assess the effect of food on the bioavailability of DNG from a final tablet formulation in fasting versus post-prandial states. The study was performed in 22 healthy male volunteers aged 18 – 40 years, with serum levels of DNG collected up to 48 hours post dose, and assessed by RIA with LLOQ 0.2ng/mL. There was a 7 day washout period between each dose. The mean pharmacokinetic parameters of DNG in this study are summarised in Table 2. The relative bioavailability of DNG from the tablet formation compared to the suspension was 100% (90%-CI: 95.3 – 106), showing that DNG is completely released from the tablet formulation. The bioavailability ratios of fasting versus fed state were within the equivalence range of 80 – 125%, which would demonstrate that food has little effect on the bioavailability of DNG. Some aspects of this study are also described in Section II *Quality Findings.*

Table 2.

TT 8: **Mean PK parameters of DNG obtained in healthy young men after single oral administration of 2 mg DNG as a tablet (fasted and fed) and as microcrystalline suspension (fasted)**

Study report BO08 (5.3.1.1 BO08)

Parameter	Unit	2 mg DNG tablet (fasted) (N = 24)	2 mg DNG tablet (fed) (N = 24)	2 mg DNG MCS (fasted) (N = 22)
C_{max}	ng/mL	39.6 (26.4)	37.3 (18.4)	45.4 (19.4)
t_{max}	h	1.75 (0.67 - 4)	2 (0.67 - 6)	0.67 (0.33 - 1.5)
$t_{1/2}$	h	8.70 (19.5)	8.76 (19.3)	8.55 (18.1)
AUC(0-t_{last})	ng·h/mL	422 (29.0)	435 (29.5)	410 (29.2)
AUC	ng·h/mL	434 (30.7)	448 (31.4)	423 (29.9)

MCS = microcrystalline suspension
For all parameters but t_{max}, the geometric mean and the geometric coefficient of variation [%] (in parentheses) are given; for t_{max}, the median and the range are provided.

Single Dose Pharmacokinetics

There are three pre GCP studies of the pharmacokinetic and metabolic pattern of tritium (^{3}H)-labelled submission DNG included in this submission.

Studies B475 and B476

This two-part pre-GCP study was carried out to investigate the PK and metabolite pattern of oral and intravenous ^{3}H-labelled DNG. The tritium was labelled in the 14α and 15α positions. It was a single centre, open-label study in 5 healthy female volunteers aged 30-38 years. In the first study period the women were given a gelatine capsule containing 101µg of labelled DNG. There was a ten week washout period after which the women were given an intravenous injection of approximately 80µg of labelled DNG in ethanol/ propylene glycol/ sorbitol solution. The maximum plasma concentration of radioactivity occurred within the first two hours. The total radioactivity in whole blood and plasma showed a parallel time course, with whole blood concentrations being less than plasma, which was taken as evidence that there was not concentration of radioactivity into erythrocytes.

The plasma elimination half-life of total radioactivity was 11.7h after oral dosing and 12.6 h after IV administration. The half life of the freely extractable fraction was 8.4h and 9h respectively. The AUC of the freely extractable fraction was 65% of the AUC of total radioactivity. These differences were attributed to the hydrophilic metabolite fraction.

After oral dosing, a maximum DNG concentration of 1.78ng/mL occurred after 1h. The fraction of unchanged DNG in total radioactivity was 75% after 1h, 70% after 2h, 72% after 4h, 62% after 6h, 52% after 8 and 12h, 48% after 24h and 42% after 48h. An elimination half-life of DNG after oral administration of 5.9h was calculated based on a one compartment model.

After 24 hours, 54% of the orally administered dose had been renally excreted, and within 5 days, 71.9% of the administered dose had been renally excreted. Following IV administration, 50.8% had been renally excreted within 24 hours and 67.9% within 5 days. After oral administration, 10.9% of the dose had been excreted via the faecal route within 5 days compared with 12.7% following intravenous administration. Following oral administration, the total amount of radioactivity excreted in both urine and faeces by day 5 was 82.7% with a renal to faecal ratio of 6.7. Following intravenous administration, the total amount excreted was 80.6% by day 5, with a renal to faecal ratio of 5.4.

Study B478

This pre-GCP study was performed to investigate the pharmacokinetics and identify the metabolites of ^{3}H-labelled DNG following oral administration of 0.1mg/kg body weight. It was a single centre open label study involving 6 healthy women aged 20-40 years.

It was found that peak plasma levels of total radioactivity were 106 ±16ng/mL and occurred at 3-8 hours. Maximum concentration of DNG was 75 ±21ng/mL. Within the first 24h, DNG accounted for 59% of total radioactivity, and at 48h, it was 53%. Plasma elimination half life was found to be 9.7 ±2.3h. Within 6 days, 86.2 ± 13.8% of the administered dose had been excreted, mainly (63.1%) via the urine.

A series of metabolites were identified from the pooled urine samples of days 1 and 2. Approximately 1% of the total radioactivity in urinary metabolites was accounted for by unchanged DNG. The metabolite pattern in urine was predominantly of strongly polar compounds, whereas in plasma, unchanged DNG tended to predominate. The main pathways of biotransformation are hydroxylation, reduction of the 3-oxo group, aromatization of ring A, introduction of additional

double bonds, and combinations of the above reactions (based on ultraviolet (UV) absorption, mass number and empirical formulae determination).

Ascending Dose Pharmacokinetics

Study B306

This was a single centre, randomised four-way crossover study to investigate the linearity of the pharmacokinetics of DNG in the dose range of 1 – 8 mg. The study population was 14 healthy women aged 18 – 40 years, of whom 12 completed the study (one withdrew because of nausea, another due to positive HCG). The four treatments (1, 2, 4, or 8mg) were administered as a single dose in the first 7 days of the menstrual cycle for four consecutive cycles.

An overview of the results is shown in Table 3. The mean C_{max} increased in proportion to the dose administered (27.5ng/mL for DNG 1mg, 53.9 ng/mL for DNG 2mg, 101ng/mL for DNG 4mg and 212ng/mL for DNG 8mg). Similarly AUC increased in proportion to dose administered. Linear regressions performed on both of these variables yielded slopes that were not statistically different to 1. Median t_{max} values ranged from 1.5 to 2h and there was no statistical difference between doses. The mean values of $t_{1/2}$ ranged between 7.52 and 8.91 hours but there was no statistical difference between these values.

The conclusion from this study is that across the dose range of 1mg to 8mg, the pharmacokinetics of DNG are linear.

Table 3

TT 18: **Mean PK parameters of DNG after oral administration – overview across studies**

For all parameters but tmax: geom. mean and geom. coefficient of variation [%] in brackets for tmax: median and minimum – maximum in brackets

Location / report no	Subj.	Form	Dose (mg)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (ng·h/mL)	AUC/D (ng·h/mL /mg)
Women, single dose								
5.3.3.1 B276	16 f	Tbl [a]	2	46.9 (18.6)	1.5 (0.67-3)	9.17 (23.2)	518 (26.2)	259
5.3.3.4 AR34	16 pm	Tbl [d]	2	45.2 (20.9)	1.00 (0.67-6)	9.71 (19.6)	523 (24.5)	262
5.3.3.1 B306	12 f	Tbl [e]	1	*27.5 (18.9)*	1.75 (0.5-4)	*7.93 (26.9)*	*306 (21.3)*	*306*
5.3.3.1 B306	12 f	Tbl [e]	2	*53.9 (16.6)*	2 (0.75-2)	*7.52 (29.1)*	*577 (25.3)*	*289*
5.3.3.1 B306	12 f	Tbl [e]	4	*101 (10.7)*	1.53 (0.5-3)	*8.32 (26.7)*	*1153 (20.6)*	*288*
5.3.3.1 B306	12 f	Tbl [e]	8	*212 (20.7)*	1.5 (0.5-3)	*8.91 (21.8)*	*2292 (19.5)*	*287*
5.3.3.3 A00681	6 f J	Tbl [f]	0.5	*17.5 (12.6)*	*1 (0.5-1)*	*7.06 (14.2)*	*155 (22.1)*	*310*
5.3.3.3 A00681	6 f J	Tbl [f]	1	*34.7 (8.93)*	*1 (0.5-22)*	*6.65 (22.4)*	*320 (17.7)*	*320*
5.3.3.3 A00681	6 f J	Tbl [f]	2	*76.1 (19.2)*	*1 (1-2)*	*7.66 (15.9)*	*695 (16.4)*	*348*
Women, multiple dose								
5.3.3.1 B276	16 f	Tbl [a]	2 [1]	51.6 (15.6)	1.25 (0.67-6)	10.0 (17.4)	533 (23.5) [3]	267 [3]
5.3.4.1 A35653	48 pm	Tbl [a]	10 [2]	374 (19.0)	1.55 (0.54-3.08)	N/A	3623 (17.9) [3]	362 [3]
Men, single dose								
5.3.1.1 B501	20 m	Tbl [c]	2	*40.0 (18.7)*	*1.5 (0.5-4)*	*8.48 (14.4)*	*456 (18.6)*	*228*
5.3.1.1 BO08	24 m	Tbl [a]	2	39.6 (26.4)	1.75 (0.67-4)	8.70 (19.5)	434 (30.7)	217
5.3.1.1 BO08	24 m	Tbl [a]	2 [4]	37.3 (18.4)	2 (0.67-6)	8.76 (19.3)	448 (31.4)	224
5.3.1.1 BO08	22 m	MCS [b]	2	45.4 (19.4)	0.67 (0.33-1.5)	8.55 (18.1)	423 (29.9)	212

f = healthy young women, pm = healthy postmenopausal women, m = healthy young men (mainly Caucasians, unless otherwise stated), J = Japanese, N/A = Not applicable
Tbl = tablet, MCS = microcrystalline suspension
(a) uncoated tablet SH T00660A or SH T00660A
(b) microcrystalline suspension SH M00660A
(c) film-coated, gelatin-containing tablet (batch no 30901‡; the double dagger sign was added to the batch number of this formulation of 1993 to avoid any possibility of confusion with the batch number used in 2003 for a batch of SH T0066AA
(d) uncoated tablet (batch no. 660497)
(e) sugar-coated tablet M656 (batch no. 21101)
(f) film-coated tablet (Mochida formulation)
(1) 2 mg DNG once daily for 14 days.
(2) 10 mg DNG (5 tablets of 2 mg) once daily for 4 days
(3) AUC(0-24h)
(4) administered under fed conditions
Italics: arithmetic mean with arithmetic coefficient of variation [%] in brackets

Study A00681

This study was performed in Japan in 1994, and the aim was to investigate the tolerability and pharmacokinetics of a single oral dose of DNG in healthy women aged 20 – 45 years. Analysis of urinary excretion of DNG and its metabolites was also performed. It was a single centre, randomised, placebo controlled, double blind, dose escalation study with 3 dose levels. Doses administered were 0.5, 1 and 2mg of DNG. A total of 6 women in each dose group received the active medication and there were 2 women in each group who were given placebo.

There were no significant adverse events recorded and there were no abnormal laboratory parameters.

An overview of the results is shown in Table 3. The median t_{max} was 1 hour in all dose groups, and the mean plasma half life ranged from 6.66 to 7.66 hours across the dose groups. Mean C_{max} and AUC increased in proportion to dose administered, and because the t_{max}, $t_{1/2}$, and clearance were all relatively static between the dose groups, linear pharmacokinetics across the dose range 0.5mg to 2mg were concluded.

Following doses of 0.5, 1.0, and 2.0mg, respectively 9.2%, 11.8% and 7.6% of DNG was excreted unchanged, either free or conjugated. Of the other metabolites, M1 was the highest at each dose level (11.7 – 13.3%), followed by M2 (1.6 – 2.7%), and M3 (≤0.3%). After 72 hours following a dose of 0.5, 1.0, or 2.0mg, the total urinary excretion of DNG and its metabolites was 22.5%, 28.0% and 23.0%, respectively.

Multiple Dose Studies

Study B276

This was an open label study to investigate the single dose and the repeated dose (over 14 days) pharmacokinetics for the final tablet formation of DNG 2mg in 16 healthy female volunteers aged 18 – 40 years. All patients completed the study according to protocol. A single dose was administered, followed by a 5 day washout period before taking DNG 2mg for 14 consecutive days. The study drug was administered in a cycle-dependent fashion to reduce intrinsic hormonal influence, with both treatments being started in the first half of the same menstrual cycle.

The pharmacokinetic parameters after single dose and multiple dosing from this study are summarised in Table 4.

Table 4.

TT 10: **Mean PK parameters of DNG obtained in healthy young women after single and repeated oral administration of 2 mg DNG as a tablet**

Study report B276 (5.3.3.1 B276)

Parameter	Unit	2 mg DNG tablet single dose (N = 16)	2 mg DNG tablet steady state (day 14) (N = 16)
C_{max}	ng/mL	46.9 (18.6)	51.6 (15.6)
t_{max}	h	1.5 (0.67 – 3)	1.25 (0.67 – 6)
$t_{1/2}$	h	9.17 (23.2)	10 (17.4)
AUC(0-24h)	ng·h/mL	431 (21.3)	533 (23.5)
AUC	ng·h/mL	518 (26.2)	655 (29.9)
CL/F	mL/min	64.3 (26.2)	62.5 (23.5)

For all parameters but t_{max}, the geometric mean and the geometric coefficient of variation [%] (in parentheses) are given; for t_{max}, the median and the range are provided.

During the multiple dose study, analysis of the mean trough DNG concentration showed that a plateau was reached after 4 dosing intervals. This would imply that the PK parameters after 14 days would represent steady-state characteristics. The mean trough level at steady-state was approximately 8.5ng/mL. Comparison of the PK after single dose and at steady-state revealed slight accumulation of DNG during the two weeks. The AUC from 0–24 h (AUC_{0-24h}) at steady state was

1.24 times higher than AUC_{0-24h} after single dose administration. The mean accumulation ratio estimated on the basis of half lives after single dose administration was similar, that is, 1.21, implying that DNG steady-state PK are predictable from PK post single dose, and linear. This was further supported by a mass-balance factor of 1.03 which indicates that the AUC from 0–24 h (AUC_{0-24h}) at steady state is equivalent to AUC from 0 h to infinity ($AUC_{0-\infty}$) after single dose.

In summary, this study demonstrated that DNG concentrations increase in the serum during the initial phase of treatment with 2mg, and reach steady state after 4 days. The pharmacokinetics are linear, with steady state PK predictable from those obtained after single dose.

Pharmacokinetic profile of Drug

Absorption

Pharmacokinetic studies in healthy male and female volunteers showed that orally administered DNG is well absorbed. The mean bioavailability from a film-coated, gelatin-containing tablet was 90.6% (B501). Compared to a micro-crystalline suspension containing DNG, the relative bioavailability from the final, uncoated, gelatine-free tablet was shown to be 100% (90%-CI: 95.3-106), which would indicate that DNG is completely released from the tablet.

Absorption was relatively rapid, with maximum serum or plasma concentration being reached from 0.67 to 2 hours (BO08) and no clinically relevant effect of food on PK of DNG.

Dose linearity of the PK of DNG following single dose oral administration was observed in two studies (B306, A00681). Following daily administration of 2mg DNG, minor accumulation was observed (accumulation ratio of 1.24), with steady state reached after 4 days (B276).

Distribution

In vitro and *ex vivo* studies presented in the sponsor's submission, and commented upon in the sponsor's clinical summary, are reported to have shown that approximately 10% of DNG in plasma is present in the free form, with the other 90% being non-specifically bound to albumin. Unlike other progestogens, DNG does not bind to the specific transport proteins SHBG or CBG.

After IV administration of DNG 2mg in healthy young men, the mean volume of distribution was 50.4 ±7.1 L (0.66 ±0.07 L/kg) (B501). In study B476, the volume of distribution at steady state of DNG was 46L after IV administration of 85µg ^{3}H-labelled DNG.

Metabolism

In vitro studies are reported to show that DNG is metabolised by phase I reactions such as hydroxylation and conjugation to form hydroxylated derivatives, with 6β-OH-DNG being identified as the major metabolite, with four others represented in plasma to only a minor extent. These metabolites are removed from plasma very quickly so that in plasma the predominant fraction is unchanged DNG. The Cytochrome P450 enzyme 3A4 (CYP3A4) was found to be the most active enzyme in the metabolism of DNG.

Study B478 showed that after administration of ^{3}H-DNG, the main fraction of radioactivity in plasma was unchanged DNG. Within 24h of administration, about 60% of total radioactivity is attributable to unchanged DNG, and in human plasma, there was no other major peak besides unchanged DNG.

DNG is extensively metabolised in humans, with only approximately 6-8% excreted as unchanged or conjugated DNG (A00681). In study B478, only 1% was excreted unchanged. In human urine, the most prominent metabolites were hydroxylated forms of DNG, with other forms being of minor quantity only.

Apart from one aromatic metabolite found exclusively in rats, *in vitro* studies showed that none of the metabolites of DNG had any significant binding to steroid hormone receptors, and so are not expected to exert any pharmacological action *in vivo*.

Excretion

As mentioned above, DNG is extensively metabolised and only a small fraction is excreted unchanged. In young healthy women who had been given 0.1mg/kg DNG, 63% of the administered dose had been excreted renally and 23% had been excreted in faeces within 6 days (B478). The mean renal elimination half life of the radioactivity in this study was 14.4 +2.4h.

The mean total clearance following IV administration of a single dose of 80µg to healthy young women was 5L/h (1.2 ml/min/kg) (B476); following an IV dose of 2mg to healthy male volunteers, the mean total clearance was 0.90 ±0.12 ml/min/kg (B501).

Pharmacokinetics in Special Populations

There were no studies submitted looking at pharmacokinetics in children. Since Visanne is being marketed only for women of childbearing age with endometriosis, the evaluator considers this appropriate.

There were no studies performed in patients with impaired liver function, because presence of impaired hepatic function in considered a contraindication to Visanne. No studies were performed in patients with impaired renal function, since no special risk was expected due to the extensive metabolism of DNG prior to excretion and the pharmacological inactivity of these metabolites.

Pharmacokinetics Summary

- *Visanne is absorbed rapidly after oral administration with a high bioavailability of ~90% (B501, BO08). There was no effect of food on the pharmacokinetics.*
- *DNG exhibits linear dose related pharmacokinetics in the range 0.5 – 8mg daily (A00681, B306)*
- *There was accumulation with repeated dosing (accumulation ratio 1.2) with steady state being reached after 4 days (B276). Terminal half life is 8 – 10 hours.*
- *In plasma, approximately 10% exists unbound in the free form, and the remainder is non-specifically bound to albumin.*
- *DNG is metabolised by the CYP3A4 system, and therefore its steady state concentrations are significantly reduced with concomitant administration of cytochrome P450 enzyme system inducers (for example rifampicin; A24058) and are significantly increased with concomitant administration of enzyme inhibitors (for example, ketoconazole, erythromycin; A30020).*
- *DNG is extensively metabolised by hydroxylation and conjugation, and these metabolites are predominantly renally excreted. DNG metabolites were not pharmacologically active.*

Drug Interactions

There were four drug interaction studies. Study AR34 is provided to demonstrate the bioequivalence of DNG alone compared to the fixed combination with oestradiol valereate (EV), which is of relevance due to the fact that other drug interaction studies are performed using the combination of DNG + EV, rather than DNG alone. Like other progestogens, DNG is metabolized mainly by the cytochrome P450 enzyme CYP3A4, so drugs interfering with this system could be expected to alter serum levels of DNG. Therefore study A24058 investigated the effects of a CYP3A4 inducer and study A30020 investigated the effects of CYP3A4 inhibitors.

Study B463 investigated DNG in combination with ethinyloestradiol (EE) for the development of a combination oral contraceptive containing DNG 2mg and EE 0.03mg, and was included in this submission for completeness. The study investigated the effect of the combination of DNG and EE

on nifedipine metabolism. This study has not been evaluated in this report because it is difficult to extrapolate any effects observed to DNG alone.

Study AR34

This was an open label, randomised, double crossover trial to investigate the bioequivalence of DNG 2mg given as a single substance in comparison to DNG 2mg given in a fixed combination with EV 2mg, following single dose administration. There was an appropriate washout period of a week between treatments. There were 16 healthy post-menopausal women enrolled in the study group aged between 52 and 72 years.

The mean pharmacokinetic parameters are summarised in Table 5. The 90%-CIs calculated for AUC and C_{max} ratios (DNG alone/ DNG+EV) were within limits of acceptance for bioequivalence with AUC ratio 104% (90%-CI: 97.0 – 111) and C_{max} ratio 107% (90%-CI: 100 – 114). It was concluded from these data that there was no significant difference in the pharmacokinetics of DNG when administered as a single substance compared to when given in fixed combination with EV 2mg, that is, bioequivalence was demonstrated. This result is used to justify application of other conclusions drawn from studies which investigated DNG in combination with EV, to preparations containing DNG alone.

Table 5

TT 11: Mean PK parameters of DNG obtained in healthy postmenopausal women after single oral administration of 2 mg DNG alone and in combination with 2 mg EV

Study report AR34 (5.3.3.4 AR34)

Parameter	Unit	2 mg DNG tablet (N = 16)	2 mg DNG / 2 mg EV tablet (N = 16)
C_{max}	ng/mL	45.2 (20.9)	42.2 (15.3)
t_{max}	h	1.00 (0.67-6)	1.00 (0.67-3)
$t_{1/2}$	h	9.71 (19.6)	10.1 (27.5)
AUC(0-t_{last})	ng·h/mL	482 (22.3)	458 (28.5)
AUC	ng·h/mL	523 (24.5)	504 (31.9)

For all parameters but t_{max}, the geometric mean and the geometric coefficient of variation [%] (in parentheses) are given; for t_{max}, the median and the range are provided.

Study A24058

This was a one-armed, open-label, non-randomised study to investigate the effect of cytochrome P450 enzyme CYP3A4 induction by rifampicin on the steady state PKs of DNG + EV. There were 16 healthy, post-menopausal women included in the study, aged from 54 to 64 years. This study was performed as part of a PK investigation into a new combined oral contraceptive regimen. This is why a combination of 2mg EV and 3mg DNG was used. The findings have now been extrapolated for use in the development of DNG as monotherapy for endometriosis.

Each patient was given one tablet of study medication (containing 2mg EV and 3mg DNG) every day for 17 days. On Days 12-16 inclusive, they were also to receive 600mg rifampicin. The steady state 24 hour PK profiles of DNG and EV were to be analysed on Day 11 and Day 17 (after 5 days treatment with rifampicin). 24-hour urine collection was performed on Days 11 and 17 for determination of 6 β-OH cortisol which is a measure of CYP induction in the liver. There were no drop-outs from the study, and no serious, severe or significant AEs were recorded.

Steady state of DNG and EV was reached at least within 10 days as evidenced by stable mean trough levels, and successful induction of CYP3A4 by rifampicin was confirmed by increased urinary 6 β-OH cortisol/ cortisol ratio between Day 11 and 17.

The mean pharmacokinetic parameters of DNG after repeat daily doses of DNG 3mg + EV 2mg before (Day 11) and after (Day 17) concomitant rifampicin administration are summarised in Table 6. Statistical comparison of the mean AUC and C_{max} was performed. The geometric mean ratio of AUC (Day 17 versus Day 11) was 17% (90%-CI: 15.6 – 18.7). The geometric mean ratio of C_{max} (Day 17 versus Day 11) was 48% (90%-CI: 44.8 – 51.6). This demonstrates a clinically significant drug interaction with concomitant administration of rifampicin leading to significant decreases in steady state concentrations and systemic exposure to DNG. Similar results were also seen with EV.

Table 6.

TT 12: **Mean pharmacokinetic parameters of DNG obtained in healthy postmenopausal women after repeated once-daily administration of 2 mg EV / 3 mg DNG tablets without and with co-administration of rifampicin (600 mg/d, day 12 – 17)**

Study report A24058 (5.3.3.4 A24058)

Parameter	Unit	Without co-administration Day 11 (N = 16)	With co-administration of rifampicin Day 17 (N = 16)
C_{max}	ng/mL	72.3 (14.8)	34.8 (20.3)
t_{max}	h	1 (0.5 - 3)	0.51 (0.49 - 1.02)
AUC(0-24h)	ng·h/mL	651 (25.2)	111 (27.2)

For C_{max} and AUC(0-24h) the geometric mean with the geometric coefficient of variation (in parentheses) are given, for t_{max} the median and the range (in parentheses) are provided.

Study A30020

This was an open-label, two-group, one-way crossover study to evaluate the effect of the known CYP3A4 inhibitors ketoconazole and erythromycin on the steady-state PK of DNG and EV. This study was performed as part of a PK investigation into a new combined oral contraceptive regimen. This is why a combination of 2mg EV and 3mg DNG was used. The findings have now been extrapolated for use in the development of DNG as monotherapy for endometriosis. There were two groups of 12 healthy post-menopausal women enrolled aged 49 to 70. All patients in both groups received one tablet containing 3mg DNG + 2mg EV per day for a total of 14 days. The patients in Group 1 received an oral dose of 400mg ketoconazole once daily for 7 days on Days 8-14 inclusive. Patients in Group 2 were given an oral dose of erythromycin 500mg three times daily for 7 days from Days 8 – 14 inclusive.

After repeat daily dosing of 3mg DNG + 2mg EV without and with concomitant oral ketoconazole, the geometric mean ratio for C_{max} (with versus without ketoconazole) was 194% (90%-CI: 184-205), and the geometric mean for AUC (with versus without) was 286 (90%-CI: 263 – 311) (Table 7). Regarding concomitant erythromycin, the geometric mean ratio for C_{max} (with versus without erythromycin) was 133% (90%-CI: 123 – 144), and the geometric mean for AUC (with versus without) was 162% (90%-CI: 146 – 180) (Table 8).

Table 7.

TT 14: **Mean pharmacokinetic parameters of DNG obtained in healthy postmenopausal women after repeated once-daily oral administration of 2 mg EV / 3 mg DNG without and with co-administration of ketoconazole (400 mg/d, day 8 - 14)**

Study report A30020 (5.3.3.4 A30020)

Parameter	Unit	Without co-administration Day 7 (N = 12)	With co-administration of ketoconazole Day 14 (N = 12)
C_{max}	ng/mL	86.7 (18.0%)	168 (24.7%)
t_{max}	h	1 (0.5 - 2)	1.75 (1 - 8)
AUC(0-24h)	h·ng/mL	838 (27.9%)	2393 (33.5%)

Table 8.

TT 15: **Mean pharmacokinetic parameters of DNG obtained in healthy postmenopausal women after repeated once-daily oral administration of 2 mg EV / 3 mg DNG without and with co-administration of erythromycin (500 mg three times a day, day 8 - 14)**

Study report A30020 (5.3.3.4 A30020)

Parameter	Unit	Without co-administration Day 7 (N = 12)	With co-administration of erythromycin Day 14 (N = 12)
C_{max}	ng/mL	87.4 (15.8%)	116 (15.5%)
t_{max}	h	1 (0.5-2)	1 (0.5-2)
AUC(0-24h)	h·ng/mL	797 (29.5%)	1290 (22.2%)

These results demonstrate a significant drug-drug interaction between EV+DNG tablets and the CYP3A4 inhibitors, ketoconazole and erythromycin. Concomitant administration of either ketoconazole or erythromycin, with DNG+EV tablets led to mild to moderate increases in concentration and systemic exposure for DNG. Similar results were seen on analysis of the PKs of oestradiol.

Pharmacodynamics

DNG is a derivative of 19-nortestosterone which is a novel compound in that it has a cyanomethyl group rather than ethinyl group at the 17alpha position. It is the first nortestosterone derivative to display no androgenic activity. *In vitro* and *ex vivo* studies report that it actually has an anti-androgenic activity of approximately one-third that of cyproterone acetate. DNG binds to the progesterone receptor of the human uterus with only 10% of the affinity of progesterone, has no binding affinity to the mineralocorticoid receptors and binds with relatively poor affinity to glucocorticoid and androgen receptors.

There were six clinical pharmacodynamic studies submitted for evaluation which are summarised below.

Healthy Volunteer Pharmacodynamics

There were five pharmacodynamic studies in healthy volunteers submitted for evaluation.

Study B468

This was a study performed in two parts to determine firstly the antigonadotrophic activity of DNG and also to determine the transformation dose of DNG, that is the progestogen dosage for the complete secretory transformation of the endometrium.

Antigonadotrophic activity

This part of the study was to investigate the antigonadotrophic effect of DNG and compare it to levonorgesterel (LNG). The study was a multi centre, open label study in which 21 women (10 eumenorrhoeic and 12 oophorectomised) between 19 and 51 years of age were enrolled. Following an observation cycle with no steroid medication, 11 women received 0.2mg DNG or 0.2mg LNG per day over 21 days, and 10 women received 0.4mg DNG or 0.4mg LNG per day over 21 days from day 5 of their menstrual cycle. For the second treatment cycle, the women who received DNG in the first cycle received the same dose of LNG and vice versa.

The results were analysed separately for eumenorrhoeic and oophorectomised women. In the 12 eumenorrhoeic women, the basal LH was suppressed in 10 out of 10 (2 patients unregistered) after LNG and 10 out of 12 patients on DNG. There was no discernible suppression in 2 women whilst on DNG. The basal FSH values were reduced in 9 out of 10 women on LNG and 11 out of 12 women on DNG. For technical reasons, progesterone could only be measured in 4 women, and was suppressed in all of them. The investigators concluded from these data that LNG at the same dose had higher antigonadotrophic effect than DNG. On analysis of the vaginal smears, the mid-cycle proliferation was lower under DNG than LNG.

For the oophorectomised women, no effect on hormone levels or vaginal cytology was detected, leading the investigators to conclude that the progestogen dose chosen had been too low for this target population. There were no significant abnormalities in other standard laboratory or clinical parameters.

Determination of transformation dose

This second part of the study was to investigate the endometrial transformation dose of DNG and compare it to LNG in post-menopausal women. The study was performed in two parts, as a multi-centre, open labelled study in healthy post menopausal women.

For the first phase, a total of 30 women were enrolled, who had received no hormone medication for at least 12 months prior to the beginning of the study. All of the women were given doses of EE 50µg daily for 26 – 28 days. From days 13 – 26 or 15 – 28 of the cycle, 18 women were given DNG and 12 women were given LNG in daily doses of 0.1, 0.25, or 0.35mg. The reason for the difference in duration and timing between 26 and 28 days was stated as being due to unavailability of testing on weekends. An endometrial biopsy was performed on the final day of treatment with both progestogens.

In the second phase of the study, 14 women were included. Again, all women were given 50µg EE daily for 28 days, and for days 15 – 28 of the treatment cycle, women were also given DNG in daily doses of 0.35,0.45, 0.55mg. In this second phase, an endometrial biopsy was also taken at the end of the oestrogen only phase to confirm a proliferative status.

In both phases, during the treatment, anti-oestrogenic activity of the progestogens was determined from vaginal smear and analysis of the cervical index and vaginal functional cytology. Clinical and standard laboratory investigations were performed at inclusion, after the oestrogen only phase, and at the end of treatment.

The administration of LNG 0.25 or 0.35mg daily resulted in the histological pattern of complete secretory transformation in all patients. An abortive secretory phase was seen in two women with

0.1mg daily LNG. With regards to DNG, full secretory transformation was seen at the dose of 0.45mg daily. Maximum oestrogen activity was seen at the end of the oestrogen only phase at Day 12 – 14, and administration of either progestogen led to almost equally changed cervical index, signifying anti-oestrogenic activity. Both treatments were well tolerated.

Study A03128

The aim of this study was to determine the dose of DNG which would lead to secretory transformation of the endometrium in post-menopausal or oophorectomised women who had been primed with ethinyloestradiol (EE). It was an open randomised parallel study design with four treatment arms.

A total of 40 women were enrolled, (10 in each arm) aged between 46 and 58 years, with no significant demographic differences between the groups. There was one drop out due to an Adverse Event (AE); severe breast pain) after 14 days treatment with EE. All women received 50ug EE daily for 14 days followed immediately by a combination of 50µg EE + 0.25, 0.35, 0.45 or 0.55 DNG respectively. Endometrial biopsy was taken on Day 15 (after the oestrogen phase) and day 29 (end of treatment), and analysed in a central laboratory.

The results of this study suggest that DNG produced progestogenic effects across all doses used during the study. Some secretory transformation was observed in 6 out of 8 analysable samples (75%) from volunteers receiving the lowest dose of 0.25mg DNG per day. However there was no clear cut increase in efficacy observed as the dose was increased. At doses of 0.35, 0.45 and 0.55mg, secretory transformation was seen in 70%, 67% and 80% of analysable cases respectively (Table 9). Therefore, the exact minimum transformation dose could not be defined in this study. There were no Serious Adverse Events (SAEs) and no significant change in any laboratory parameter.

Table 9.

Text Table 3: Frequency of endometrium transformation in volunteers from 4 treatment groups after administration of daily doses of 0.05 mg EE (14 days) and 0.05 mg EE + 0.25 mg, 0.35 mg, 0.45 mg, or 0.55 mg DNG (14 days) (intent-to-treat analysis)

		Endometrium amount not		Transformation type					Secretory transf.
Dose group	N_v	sufficient for assessment	N_s	No transf.	Partial / topographic	Partial / gland (1)	Partial / stroma (2)	Full transf. (3)	N (1+2+3)
0.25 mg DNG	10*	1	8	0	2	3	0	3	6
0.35 mg DNG	10	0	10	3	0	1	1	5	7
0.45 mg DNG	10	1	9	1	2	1	4	1	6
0.55 mg DNG	10	0	10	2	0	0	3	5	8

Legend:
N Number of samples exhibiting endometrium transformation of type 1 to 3
N_v Number of volunteers
N_s Number of analyzable biopsy samples
transf. Transformation
*) 1 drop-out after day 14 of the study

Study B470

This study was performed to determine the ovulation inhibition dose of dienogest in healthy women. This was a single centre, open, randomised, four arm study. A total of 30 women aged

between 20 and 29 years were initially enrolled and observed for a control cycle to ensure ovulation. Nine subjects dropped out of the study (5 due to anovulatory control cycles), a total of 22 were treated with DNG and 21 completed the study (one patient withdrew due to an AE). Of these, 12 completed two treatment cycles with different doses, giving a total observed exposure to DNG of 33 menstrual cycles.

After the control cycle, patients were randomised into four groups receiving 0.5, 1, 1.5, or 2mg DNG for 21 days commencing on day 5 of their menstrual cycle. Evidence of inhibition of ovulation was taken as progesterone levels <3.5 nmol/L. If the level was 3.5 – 30nmol/L, inhibition of ovulation was judged on the total hormone profile. Progesterone levels >30 nmol/L were considered evidence of definite ovulation.

At a daily dose of 0.5mg DNG, ovulation was inhibited in 6 out of 9 cycles as determined by progesterone levels <3.5 nmol/L. The dose of 1.0mg DNG definitely inhibited ovulation in 7 out of 8 cycles. In the other patient, it is reported that analysis of her hormone profile and the timing of her medication led the investigators to deduce that her assumed "menstrual bleed" which she took as Day 1 of her cycle for study purposes may have been a late-follicular phase intermenstrual bleed. Despite no manifest LH peak in this case, it was assumed that ovulation or luteinisation of a follicle must have occurred, leading to the rise in progesterone. It was therefore stated in the report that this patient did not take the DNG in a cycle-conform manner and so she was excluded from analysis. At doses of 1.5mg (n=8) and 2.0mg DNG daily (n=8), inhibition of ovulation was demonstrated.

DNG doses of 0.5 – 1.5mg daily led to follicular maturation in most cycles as evidenced by a rise in oestradiol concentration. Even with the highest dose of 2mg, follicular growth was only apparently prevented in 4 out of 8 women.

The frequency of dysmenorrhoea decreased in the treatment cycles compared with the control cycles, although the frequency of additional bleeding increased.

After the exclusion from analysis of the subject in whom there was doubt about the cycle-conformity of her progestogen exposure, it was concluded according to measured values for progesterone, oestradiol, FSH and LH that DNG in a dose greater or equal to 1.0mg inhibited ovulation. It was also derived from the oestradiol concentrations that follicular maturation is not completely suppressed even at doses of DNG 2mg daily.

It is the opinion of the evaluator that on the basis of a single presumed cycle error, the data from that patient should not have been excluded, and the conclusion that the dose of 1.0mg safely inhibits ovulation cannot be definitively reached. The evaluator agrees that at doses of 1.5mg DNG and greater, there is evidence of ovulation inhibition in all women in this relatively small sample.

Study A02263

This study was designed to investigate the effects of 2mg DNG alone and a combination of 2mg DNG with 30µg EE on gonadotrophin secretion (FSH, LH), and its pulsatile character. It was a single centre, open, two arm study. A total of 15 previously healthy women aged 21 – 32 years were included in the study (7 in the DNG group and 8 in the DNG+EE group). Ten of these women (3 from the DNG group and 7 from the DNG+EE group) went through a prior untreated control cycle.

The study drugs were then administered once daily for 21 days beginning on Day 1 of the menstrual cycle. The target parameters were measured on the $5^{th}/6^{th}$ and $21^{st}/22^{nd}$ Day of the control and treatment cycles.

Administration of 2mg DNG alone altered neither the pulsatility nor the hypophyseal gonadotrophin secretion in comparison with the early follicular phase, so antigonadotrophin effects could not be verified. There was no evidence of ovulation in any of the subjects taking DNG alone, as evidenced

by the very low progesterone levels measured on day 21. After administration of DNG for 21 days, only follicles ≤10mm were observed, leading to the conclusion that whilst follicular maturation was not completely suppressed, it was arrested by administration of DNG.

Results for DNG+EE combination revealed inhibition of hypophyseal gonadotrophin release and its pulsatility, and also inhibited ovulation.

Study A35653

The aim of this study was to investigate the potential of a fixed combination of 3mg DNG and 2mg EV to delay cardiac repolarisation (as evidenced by prolongation of QT interval on ECG) in healthy postmenopausal women. Secondary aims were to evaluate the PK of DNG, oestradiol and oestrone. The study was performed as a double-blind, double-dummy, placebo-controlled, four-way cross over trial. The four treatments investigated were: 1) therapeutic DNG dose (combination 3mg DNG + 2mg EV) once daily for 4 days, 2) supratherapeutic DNG dose (5 x 2mg DNG) once daily for 4 days, 3) negative control (placebo) once daily for 4 days, and 4) positive control (single dose of 400mg moxifloxacin) – known to cause prolongation of QT interval.

A total of 55 women were randomized, but only 40 completed the study as per protocol. After the final dose of the study drug, blood samples and regular ECGs were performed and analysed. There was a washout period of at least 10 days between each study medication.

There was no prolongation of mean values for QT interval (uncorrected, or corrected via various methods) observed with either preparation containing DNG at any time point. The comparison of these two substances with placebo showed no significant difference in change in QT. It was therefore concluded that DNG had no effect on cardiac repolarisation.

DNG administered as a 10mg oral dose displayed similar PK parameters as compared to the combination 3mg DNG + 2mg EV when the dose was normalised to 3mg DNG.

Both DNG preparations were well tolerated in this study.

Patient Pharmacodynamics

There is one study (A05436) submitted and described as a pharmacodynamic study in patients and is described below. Study A02266 is evaluated in the efficacy section of this evaluation, but this study was also described in the submission as a dose finding study, upon which the decision to use the dose of DNG 2mg daily in the pivotal efficacy trials was based.

Study A05436

This study was performed to compare the efficacy of DNG to that of leuprorelin acetate (LA) in preparing the endometrium for endometrial ablation in cases of refractory uterine bleeding, that is, to investigate whether DNG leads to sufficient endometrial suppression. The study was performed as an open, randomised, controlled parallel study.

The patients were assigned to one of two treatment groups, one receiving DNG 2mg daily for 56 days, the other receiving two intramuscular (IM) injections of LA 3.75mg with a 28 day interval between the injections. Surgery was planned by means of roller ball ablation on Day 56, with the patients being assessed on the day of surgery by histological analysis, visual assessment at hysteroscopy and surgeons' overall assessment of endometrial preparation (primary variables), as well as by trans-vaginal ultrasound and measurement of endometrial thickness.

A total of 75 women with refractory uterine bleeding (and malignant cause excluded) were enrolled, 37 in the DNG group and 38 in the LA group. One patient from each group did not complete the study because they withdrew their consent.

There was no significant difference in histological findings of the endometrium at time of ablation. Regarding the surgeon's assessment, pre-treatment with LA was found to be superior, with 84.2% of cases being described as "optimal", compared to 52% for DNG. However, when the assessment categories "optimal" and "sufficient" were combined, there was little difference with 92.1% in these two categories for LA, and 91.7% in the DNG group. On hysteroscopic evaluation, there was a statistically significant difference in the appearance of the endometrial cycle phase only, with LA being superior to DNG. On ultrasound, there was a more pronounced reduction in endometrial thickness with LA (-57%) compared to DNG (-38%). The bleeding patterns also seemed more favourable with LA compared to DNG, with only 36.8% of the LA group having bleeding at the end of treatment compared to 75% in the DNG group, although this was mostly only spotting or light bleeding.

Pharmacodynamics Summary

- *Despite only binding to the progesterone receptor of the human uterus with 10% of the relative affinity of progesterone, DNG has progestogenic actions as evidenced by the dose required to induce endometrial transformation. Effects were seen even at the lowest dose evaluated of 0.25mg/day (A03128). In study B468 complete secretory transformation was achieved with daily dose DNG of 0.45mg. However, in study A03128, a complete transformation was not achieved with any dose up to 0.55mg DNG daily, although even at the lowest dose investigated (0.25mg daily) clear progestogenic effects were noted.*
- *There was minimal effect on hypophyseal gonadotrophin secretion or pulsatility in comparison with the early follicle phase after the administration of DNG 2mg alone observed in study A02263. However, in study B468 antigonadotrophic effects were observed in eumenorrhoeic women, but not in oophorectomised women with low doses of 0.2mg and 0.4mg DNG. These effects were less pronounced with DNG compared to LNG.*
- *Inhibition of ovulation was observed in all women who took $\geq$1.5mg DNG daily. Follicular maturation was halted but not completely suppressed even in women treated with the highest dose of DNG 2mg daily. (B470, A02263)*
- *DNG 2mg daily caused sufficient endometrial suppression to provide adequate endometrial preparation prior to ablation surgery. However, it was not as effective as LA in this regard (A05436).*
- *There was no observed effect on cardiac repolarisation with DNG at doses in the therapeutic range or at supratherapeutic dose range with QT intervals remaining unchanged after treatment (A35653).*
- *At a dose of DNG 2mg daily, ovulation is inhibited, but ovarian hormone production is not completely suppressed.*

Efficacy

Overview

Data of eight phase 2/3 trials were submitted to support the efficacy of Visanne in the treatment of endometriosis involving 715 women treated for 12 to 64 weeks.

There were three clinical phase 3 trials, two of which were considered pivotal. Study A32473 compared the efficacy of Visanne versus placebo in reducing symptoms of endometriosis. Study AU19 was designed to investigate the non-inferiority of Visanne in comparison to the GnRH analogue LA in reducing symptoms of endometriosis. Study A39700 was a one-year extension to the study A32473 to evaluate menstrual bleeding patterns and sustained improvement in symptoms.

Data from three phase 2/3 trials were submitted to demonstrate efficacy of Visanne in reduction of endometriotic lesions using surgical methods. Study A02266 was a phase 2 dose finding study to assess the efficacy of Visanne in comparison to 1mg and 4mg DNG in reduction of endometriotic

lesions. Studies A01177 and A01176 were early pre-GCP studies, assessing endometriotic lesions before and after treatment.

The efficacy data of two additional clinical studies were included for completeness (Study A04431 and Study B567). These used different study populations and dosage and so have not been evaluated for efficacy but safety results are presented below (see *Safety*).

Pivotal Trials

Study A32473

Study Design and Patient Characteristics

This is a multi-centre, double blind, randomised, placebo controlled, parallel-group, phase 3 trial in women of reproductive age, evaluating the efficacy of dienogest (DNG) 2mg daily in reducing symptoms of endometriosis compared with placebo over 12 weeks. From a planned study size of 176 patients, 215 patients were screened, with a total of 198 being randomised and included in the study as the full analysis set (FAS). The study was conducted between March 2004 and September 2006, and was conducted in accordance with GCP principles. The primary efficacy endpoint was reduction of EAPP, with secondary efficacy outcomes including intake of rescue medication, B&B severity profile for symptoms and quality of life (SF-36) assessment.

Women of child bearing age between 18 and 45 were recruited. To be included they had to complain of pain associated with histologically-proven endometriosis (stages I- IV according to r-ASRM[xv] score), as determined by diagnostic laparoscopy within 12 months prior to onset of treatment but no later than 6 weeks prior to screening. They had to have a baseline pain score (on VAS) of at least 30mm and be willing to use barrier contraception. Exclusion criteria included previous use of hormonal agents (GnRH agonists within 6 months, progestins and danazol within 3 months, oral contraception within 1 month prior to screening), pregnancy or lactation, abnormal cervical smear, or significant medical comorbidity (significant ischaemic heart disease, cerebrovascular disease, hypertension, metabolic disorders, history of malignancy and so on) .

Patients and investigators were blinded as to the nature of the medication. As one arm of the study was placebo, it was anticipated that a considerable amount of analgesia may be used by the placebo patients and possibly also the patients receiving DNG. To facilitate accounting and analysis of analgesia used for EAPP, rescue medication in the form of ibuprofen 400mg tablets was distributed to all patients. In order to monitor compliance, patients were required to complete a daily diary detailing the medication used (DNG, placebo and ibuprofen) and all used, partly used and unused medication packages were returned to the investigator.

Patients had their pelvic pain assessed by VAS at baseline, and every 4 weeks until end of treatment (EOT). Their symptoms and signs were assessed by B&B scoring at baseline and EOT, as was their quality of life using the SF-36 questionnaire. Furthermore, both patient and investigator were asked to give a global assessment of the study treatment by means of a Clinical Global Impression (CGI) score at EOT.

Overall, 198 patients were randomised, with 102 receiving DNG 2mg daily and 96 receiving a daily placebo, making up the FAS. Both groups were well matched in terms of general demographics, medical, surgical and gynaecological history.

The frequency of distribution of patients according to the r-ASRM stages of endometriosis was comparable between the two groups (Table 10), as was the mean baseline VAS (placebo 57.0mm and DNG 56.8mm). There were 81 patients with overall protocol deviations in the placebo group, with 26 of these patients having what were defined as major protocol deviations, excluding them from the per protocol set (PPS). In the DNG group there were 80 patients with overall protocol

deviations, 28 of these defined as major. So from the original patients randomised to the FAS, this left a PPS of a total of 144 patients, 70 in the placebo group and 74 in the DNG group. There was only one case of drop out due to insufficient efficacy, which occurred at day 46 in the placebo group.

Table 10. Study A32473

Frequency of laparoscopically-confirmed endometriosis and r-ASRM stage - FAS

		Placebo	DNG
Laparoscopy available (yes)		**96 (100.%)**	**102 (100.0%)**
Endometriosis histology available (yes)		**95 (99.0%)**	**99 (97.1%)**
r-ASRM stage	**I**	**8 (8.3%)**	**13 (12.7)**
	II	**19 (19.8%)**	**17 (16.7%)**
	III	**43 (44.8%)**	**46 (45.1%)**
	IV	**25 (26.0%)**	**26 (25.5%)**

Primary Efficacy Outcomes

The primary objective of this study was to prove the superiority of 2mg daily DNG for the treatment of endometriosis associated pelvic pain (EAPP) in comparison to placebo. EAPP was assessed by the target variables of change of VAS (in mm) and change of intake of rescue medication (cumulative over the preceding 28 days) between baseline and EOT. Using an error margin alpha = 0.025 for one-sided test, and a power of 0.9, it has been calculated that it was necessary to evaluate 66 patients in each arm to prove superiority of DNG to placebo. With an expected drop out rate of 25%, a total of 176 patients needed to be evaluated to ensure a power of 0.9.

To account for multiple endpoints, the 3 step hierarchical testing procedure of Rohmel and others[xxiv] was employed, which consists of 1) demonstration of non-inferiority, 2) Laeuter's one sided standard sum test for overall demonstration of superiority of DNG over placebo and 3) test of superiority of DNG versus placebo for each of the two primary variables.

In terms of change in VAS at EOT, placebo and DNG were both characterised by a reduction of mean VAS values for EAPP. The reduction observed in the DNG group (-28.8 ±24.5mm and -27.4 ±22.9mm without and with LOCF, respectively) was more pronounced than in the placebo group (-16.9 ±16.0mm and -15.1 ±16.4mm without and with LOCF, respectively) (Table 11). The difference between the means (placebo minus DNG) in the LOCF analyses was 12.27 – in favour of DNG – with 95% confidence interval (CI) between 6.403 and 18.140. This 95% CI was greater than the threshold defined as clinically relevant of -15mm. The PPS analysis confirmed the FAS analysis.

Table 11. Study A32473

VAS for EAPP: Absolute values and individual change [mm] (EOT – Baseline), and 95% confidence interval – FAS

	Placebo	DNG		
VAS Baseline	57.0 ± 17.8	56.8 ± 18.0		
VAS Day 84 (EOT)	39.4 ± 22.1	27.6 ± 20.4		
Difference EOT – Baseline	-16.9 ± 16.0	-28.8 ± 24.5	Difference between means (placebo *minus* DNG)	95% Confidence interval
Difference EOT – Baseline, LOCF	-15.1 ± 16.4	-27.4 ± 22.9	12.272	6.403 to 18.140

Source: T 99 and T 104. Mean values were rounded to 1 decimal. VAS = Visual analog scale; EAPP = Endometriosis associated pelvic pain; EOT = End of Treatment; LOCF = Last-observation-carried-forward. Negative signs in group means = Improvements.

Regarding intake of rescue medication, there was a modest reduction from baseline to EOT in both groups, slightly more pronounced under DNG than placebo (-4.4 ±6.4 and -3.7 ±8.2, respectively). The difference between placebo and DNG was 0.741 in favour of DNG, with 95% CI between -1.412 and 2.895. This CI was greater than the threshold regarded as clinically significant of -9 tablets (Table 12). PPS analysis again confirmed the FAS analysis.

Table 12. Study A32473

: Rescue medication for EAPP: Absolute values, individual change [number of tablets] (EOT – Baseline), and 95% confidence interval – FAS

	Placebo	DNG		
Rescue Baseline*	9.4 ± 8.6	9.9 ± 7.4		
Rescue EOT*	5.7 ± 5.8	5.5 ± 5.8		
Difference EOT – Baseline	-4.0 ± 8.7	-4.7 ± 6.5	Difference between means (placebo *minus* DNG)	95% Confidence interval
Difference EOT – Baseline, LOCF	-3.7 ± 8.2	-4.4 ± 6.4	0.741	-1.412 to 2.895

Source: T 100 and T 105. * Cumulative values for the preceding 28 days; EAPP = Endometriosis associated pelvic pain; EOT = End of Treatment; LOCF = Last-observation-carried-forward.
Negative signs in group means = Improvements.

Step 2 could then be performed to demonstrate overall superiority of DNG over placebo via the two-dimensional Laeuter's test which was significant for the FAS ($p=0.00165$) and again confirmed in the PPS ($p<0.001$).

Due to the above, step 3 was then performed to determine which of the two target variables (VAS reduction or rescue medication) were responsible for the significant effects of DNG. For VAS, the 95% CI for the difference between placebo minus DNG (6.403 to 18.140) did not contain zero ($p<0.001$); for the rescue medication the 95% CI for the difference placebo minus DNG did contain zero (not statistically significant). This shows that the statistically significant effect was attributable to pain reduction rather than the reduction in use of rescue medication. PPS analysis confirmed the FAS analysis.

In summary, the three step hierarchical analysis demonstrated the effects of DNG on reduction of EAPP were statistically superior to those of placebo, and could be attributed to reduction in pain given that the decrease in intake of rescue medication was not significantly different between the groups. Despite a noticeable placebo effect, it is the opinion of the evaluator that this reduction of

EAPP is clinically as well as statistically significant, with a difference between the mean reductions of VAS of 12.27mm. This is depicted graphically in Figure 2 and Figure 3

Figure 2.

TF 2 EAPP measured by VAS [mm] (mean ± standard error of the mean) by treatment and time – FAS (study A32473)

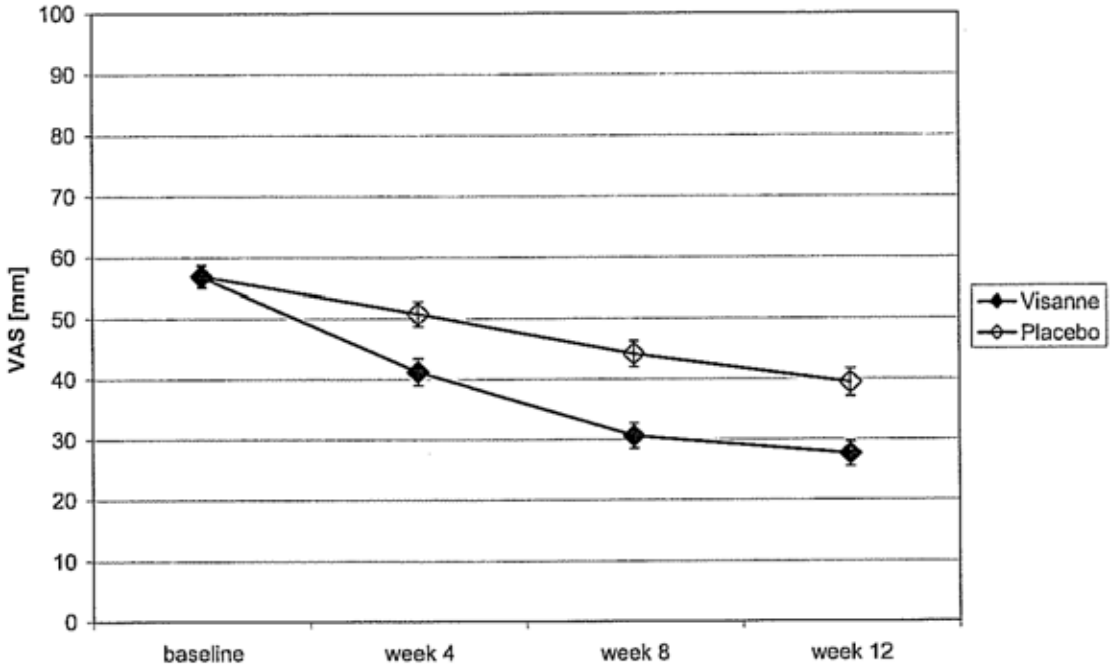
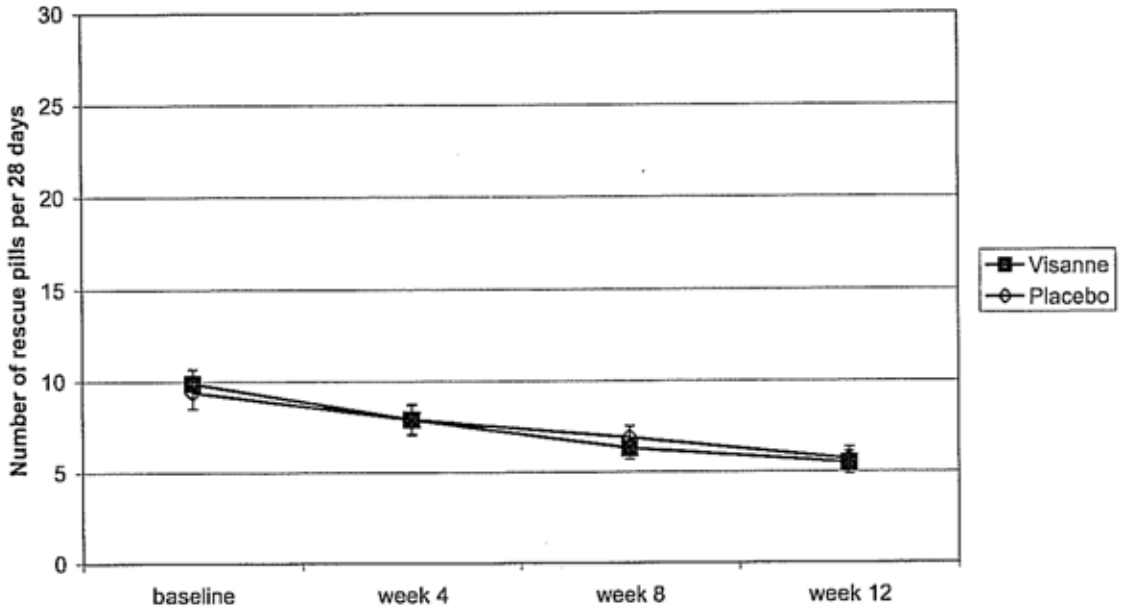


Figure 3.

TF 3 Intake of rescue medication (mean ± standard error of the mean) by treatment and time – FAS (study A32473)



Secondary Efficacy Outcomes

A sensitivity analysis was performed to look at percentage of responders versus non responders, with several categories of responders defined beforehand. Each category was based on given levels of reduction of VAS (either absolute or a percentage) and in relationship to change in rescue medication. The results show throughout the categories that the percentage of responders between the groups was higher with DNG than placebo, and the stricter the definition of responder, the greater the difference observed in the DNG group. However, no statistical analysis of these differences is presented.

A further sensitivity analysis was performed which adjusted the VAS according to intake of rescue medication. A "penalty" level was introduced for the VAS for the intake of any rescue medication (1 tablet daily equalling 20mm, 15mm or 10mm). The rationale for this was to provide some combined evaluation for the two target variables of VAS and rescue medication. At baseline, values for adjusted VAS were similar. Results are summarised in Table 13. During treatment, the values for VAS were lower in the DNG group compared with placebo for all three levels of adjustment, and this was also noticeable in the mean differences between EOT and baseline. For placebo, the differences ranged between -18.4 ±17.0 and -19.9 ±18.6, depending on adjustment conditions; for DNG these differences were between -29.2 ±24.1 and -30.0 ±25.0. There is an observed difference between these values, which suggests that DNG was more effective than placebo, but there was no statistical analysis performed on this.

Table 13.

TT 36: VAS [mm] adjusted for use of rescue medication (further sensitivity analysis) – FAS

Category of VAS adjustment	Placebo	DNG
Baseline, 1 daily tablet = 20 mm	62.8 ± 18.7	63.0 ± 18.6
Cycle 1, 1 daily tablet = 20 mm	56.5 ± 20.1	46.9 ± 24.0
Cycle 2, 1 daily tablet = 20 mm	49.1 ± 20.8	35.1 ± 22.4
EOT, 1 daily tablet = 20 mm	43.2 ± 22.7	31.7 ± 22.3
Difference EOT – Baseline, 1 daily tablet = 20 mm *	-19.9 ± 18.6	-30.9 ± 25.0
Baseline, 1 daily tablet = 15 mm	61.1 ± 18.2	61.2 ± 18.2
Cycle 1, 1 daily tablet = 15 mm	55.1 ± 19.9	45.5 ± 23.4
Cycle 2, 1 daily tablet = 15 mm	47.9 ± 20.6	34.0 ± 21.8
EOT, 1 daily tablet = 15 mm	42.2 ± 22.5	30.8 ± 21.8
Difference EOT – Baseline, 1 daily tablet = 15 mm *	-19.2 ± 17.8	-30.1 ± 24.5
Baseline, 1 daily tablet = 10 mm	59.4 ± 17.8	59.4 ± 17.8
Cycle 1, 1 daily tablet = 10 mm	53.7 ± 19.7	44.1 ± 22.8
Cycle 2, 1 daily tablet = 10 mm	46.6 ± 20.5	32.9 ± 21.4
EOT, 1 daily tablet = 10 mm	41.2 ± 22.3	29.8 ± 21.3
Difference EOT – Baseline, 1 daily tablet = 10 mm *	-18.4 ± 17.0	-29.2 ± 24.1

Source: T 112. Values were rounded to 1 decimal. VAS = Visual analog scale; EOT = End of Treatment.
* Negative signs = Improvements. Detailed definitions of VAS adjustments are provided in TT 20.

Decrease in VAS for EAPP over time was another secondary outcome variable and consistent with the primary analysis; mean VAS underwent a progressive decline in both placebo and DNG groups, but the decline in VAS for DNG was more pronounced than placebo throughout the treatment, although no statistical analysis is offered (Table 14**)**.

Table 14. Study A32473

VAS for EAPP: Time course – FAS and PPS

	FAS		PPS	
	Placebo	DNG	Placebo	DNG
VAS Baseline	57.0 ± 17.8	56.8 ± 18.0	56.4 ± 16.7	57.7 ± 16.4
VAS Day 29	50.8 ± 19.6	41.2 ± 22.0	50.6 ± 18.5	44.5 ± 21.1
VAS Day 57	44.2 ± 20.5	30.6 ± 20.6	44.4 ± 19.8	31.7 ± 19.9
VAS Day 84 (EOT)	39.4 ± 22.1	27.6 ± 20.4	40.1 ± 21.4	28.5 ± 19.8

Source: T 99 and T 101. Values were rounded to 1 decimal. VAS = Visual analog scale;
EAPP = Endometriosis-associated pelvic pain; EOT = End of Treatment. Decreases over time = Improvements.

The intake of rescue medication also underwent a modest decline during treatment in both groups. As can be seen in Table 15, there is no discernible difference over time between DNG and placebo, although again, no statistical analysis was performed.

Table 15. Study A32473

Rescue medication for EAPP: Absolute values, individual change [number of tablets] (EOT – Baseline) – FAS and PPS

	FAS		PPS	
	Placebo	DNG	Placebo	DNG
Rescue Baseline*	9.4 ± 8.6	9.9 ± 7.4	9.4 ± 6.8	10.7 ± 7.0
Rescue Cycle 1*	7.9 ± 7.6	7.9 ± 8.7	8.0 ± 6.3	8.6 ± 8.3
Rescue Cycle 2*	6.9 ± 6.1	6.3 ± 6.0	7.1 ± 5.8	6.7 ± 5.8
Rescue EOT*	5.7 ± 5.8	5.5 ± 5.8	6.3 ± 6.0	5.9 ± 5.9

Source: T 100 and T 102. Values were rounded to 1 decimal. * Cumulative values for the preceding 28 days (as by diary data); EAPP = Endometriosis-associated pelvic pain; EOT = End of Treatment.
Decreases over time = Improvements.

The B&B severity profile investigates symptoms (pelvic pain, dysmenorrhoea and dyspareunia) and signs (pelvic tenderness and induration) of endometriosis. These were analysed as sum scores for pelvic pain, physical signs score and total symptom and sign score. At baseline the frequencies of symptoms and signs were largely comparable between DNG and placebo groups. Comparing values at baseline and EOT, there was a shift from higher (severe and moderate) to lower intensities in both treatment groups. Analyses of the sum scores confirmed the trends observed for the single symptoms and signs, that is, there was a decrease in intensity over time in both treatment groups, and the shift from more severe to less severe intensities appeared more marked in the DNG group compared to placebo. However, no statistical analysis of these variables was performed.

When looking at the generic SF-36 quality of life questionnaire, there was slight improvement in both groups after 12 weeks of treatment, with no real differences between DNG and placebo noted.

Regarding the CGI, both the patient and investigator CGI after 12 weeks treatment indicated more favourable outcome after DNG than placebo, although clear placebo effects were demonstrated. Categories of "no change" or "worse" were more frequent under placebo, and "very much improved" and "much improved" were more frequent in the DNG group.

Study AU19

Study Design and Patient Characteristics

This is a multi-centre, open-labelled, controlled, and randomised, parallel-group study in women of child-bearing age. The aim is to investigate the efficacy and safety of daily oral administration of 2mg dienogest (DNG) versus IM administration of 3.75mg LA every 4 weeks in the treatment of

symptomatic endometriosis over 24 weeks. Overall, 252 patients were randomised in accordance with the planned sample size. The study was conducted between December 1998 and April 2001 in accordance with GCP guidelines. The study was designed to investigate the non-inferiority of DNG compared to LA. The primary efficacy endpoint was individual change in pelvic pain from baseline to end of treatment as assessed by VAS. Secondary efficacy variables were pelvic pain over time, changes in B&B symptom severity scoring and changes in quality of life (SF-36) from baseline to end of treatment.

Women of childbearing age between 18 and 45 years with pain associated with histologically proven endometriosis were recruited and inclusion and exclusion criteria were similar to those described in study A32473 above.

Non-inferiority between DNG and LA was defined as a difference between VAS scores at end of trial of $\leq$15mm between the LA group and DNG group. Assuming that the standard deviation of the difference in pelvic pain on the VAS between before and after treatment was 30mm, it was calculated that 88 patients were required in each group to prove non-inferiority with a power of 90%.

A total of 269 women were screened for the study, with 252 patients randomised to either DNG (n=124) or LA (n=128). Of these, 4 patients randomised to receive DNG did not take the medication leaving a total of 120 and 128 patients in the full analysis set (FAS) for DNG and LA respectively. Both groups were well matched demographically, with no significant differences in medical, gynaecological and laparoscopic history. There were 30 and 32 major protocol deviations in the DNG and placebo groups, respectively with PPS of 90 and 96 patients, respectively.

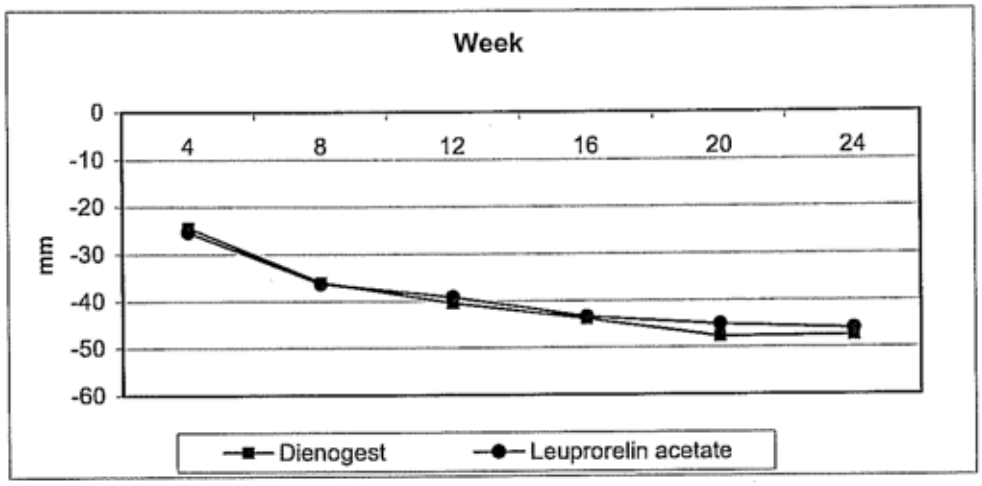
Primacy Efficacy Outcomes

The primary efficacy variable was the change in pelvic pain as assessed by the VAS after 24 weeks of treatment compared to baseline. The investigators stated that in accordance with the non-inferiority approach, this was analysed in the PPS, although analysis of the FAS was also performed to confirm robustness of results.

Regarding the PPS, at baseline the mean VAS was 60.2mm (±24.2) in the DNG group and 57.9mm (±21.0) in the LA group. After 24 weeks of treatment this had dropped to 12.7mm in the DNG group and 11.9mm in the LA group, which is a mean decrease of 47.5mm (±28.8) in the DNG group and 46.0mm (±24.8) in the LA group (see Figure 4 and Table 30 in *VI. Overall Conclusion and Risk/Benefit Assessment*) and represents a clinically significant reduction in pain in both groups.

Figure 4. Study AU19

Mean changes of the VAS (in mm) at Weeks 4, 8, 12, 16, 20 and 24 as compared to baseline (PP).



The difference between the two groups was -1.5mm (95% CI: -9.26, 6.25). With a non inferiority margin of 15mm, the hypothesis that DNG is inferior to LA is rejected, statistically confirming no-inferiority of DNG compared to LA. Similar results were also seen in analysis of the FAS. It was noted that the magnitude of the reduction in VAS is greatest in the first 4 weeks with both treatments. As the study progresses, there is still ongoing reduction in VAS out to EOT at 24 weeks with both treatments.

Secondary Efficacy Outcomes

The secondary efficacy variables were pelvic pain over time, changes in B&B symptom and sign severity scoring and changes in quality of life (SF-36) from baseline to end of treatment.

Improvement rates of VAS over time were analysed for the PPS and FAS. In the PPS, 96.7% of the DNG group and 95.8% of the LA group had an improvement in pelvic pain after 24 weeks of treatment. In the FAS, 90.7% of the DNG and 93.0% of the LA group showed an improvement. Statistical analysis demonstrated non-inferiority for DNG compared to LA (Table 16**)**.

Table 16. Study AU19

Improvement rates in the VAS between baseline and weeks 4, 8, 12, 16, 20, and 24 (PP and FAS)

Analysis Set	week	DNG group		LA group	
		Number of patients	% improved	Number of patients	% improved
PP	4	90	83.3	96	86.5
PP	8	90	87.8	96	93.8
PP	12	90	87.8	96	93.8
PP	16	90	95.6	96	96.9
PP	20	90	96.7	96	95.8
PP	24	90	96.7	96	95.8
FAS	4	115	75.7	123	81.3
FAS	8	114	81.6	124	93.5
FAS	12	112	83.0	123	94.3
FAS	16	111	88.3	119	94.1
FAS	20	110	90.9	119	92.4
FAS	24	108	90.7	115	93.0

Use of rescue medication in this study is discussed in the safety section of the submission. However, in order to fully appreciate the efficacy of both treatments, the evaluator considers that it should be mentioned when discussing efficacy. Intake of concomitant medication was checked at screening, baseline, after 12 weeks of study medication and EOT. There was no relevant difference between treatment groups regarding number of women who changed concomitant medication during the course of the study. At EOT 43.3% of women in DNG group and 42.2% of women in LA group had changed their medication compared to screening.

Special attention was given to intake of medication related to pain and there were no relevant differences described between the two groups.

There was a decrease in intensity of symptoms and signs of endometriosis as assessed by the B&B score across both treatment groups. In both treatment groups, the number of women with symptoms or findings and the intensity of the symptoms/ findings decreased over time. There was no relevant difference noted between the two treatment groups, with the percentage of patients with each severity grade over time being similar, and 22% of patients in both groups showed no symptoms.

The SF-36 quality of life questionnaire was assessed at screening and EOT, and there was a similar degree of improvement in scores for physical health and mental health in both treatment groups. At EOT, the mean score in the physical health summary scale in the FAS improved by 9.6 points and 7.1 points in the DNG and LA groups, respectively. The mean mental health summary score improved by 4.0 points and 0.9 points, respectively. No statistical comparison of these results between treatment arms is offered. Similar results were seen in the PPS.

Extension Studies: Long-term Efficacy

Study A39700

Study Design and Patient Characteristics

This was a multicentre, open, one-arm study to investigate the safety and efficacy of daily oral administration of 2mg DNG (Visanne) for the treatment of endometriosis over a period of 52

weeks. It was performed as a follow-up to Study A32473. The study was conducted between July 2004 and November 2007 in accordance with GCP guidelines.

The primary endpoint was uterine bleeding pattern, often considered a safety characteristic. This was analysed as number of bleeding/spotting days, number of bleeding/ spotting episodes, individual mean length of bleeding/spotting episodes, maximal intensity of bleeding/ spotting episodes, number of spotting only days, number of spotting only episodes, and individual mean length of spotting only episodes. The bleeding patterns were assessed using both the World Health Organization (WHO) recommended 90 day interval and also a 28 day reference period corresponding to usual cycle length. Assessment of EAPP by means of VAS was evaluated as a secondary endpoint.

Women who had successfully completed study A32473, fulfilling all compliance requirements without any major protocol deviations, were eligible for enrolment in this study. The end of study A32473 coincided with the beginning of this one-arm follow up. The initial study plan was to treat for 36 weeks but after consultation with European Medicines Evaluation Agency (EMEA) guidelines on safety requirements for long-term approval of new medications, the treatment period was amended to 52 weeks. Each patient enrolled received treatment with DNG 2mg once daily for 52 weeks after completion of medication for study A32473, with no interruptions. The patients kept a diary card to monitor bleeding pattern, compliance and also to assess EAPP by means of VAS every 28 days.

A total of 168 patients who completed study A32473 were included in this one-arm follow up and comprised the FAS. Of these 168 patients, 81 had been previously treated with placebo for 3 months and 87 patients had been previously treated with DNG for 3 months. Of these, 152 completed the study treatment while 16 patients discontinued the treatment prematurely.

Since the study was a follow up to a placebo-controlled study, the patient sample was not homogenous with respect to the previous treatment and also EAPP at the beginning of this study. As a consequence, subgroup analyses focusing on previous treatment were appropriately carried out in addition to the FAS analysis.

Primary Efficacy Outcomes

Regarding the 90 day reference period, the number (mean ±SD) of bleeding/ spotting days decreased from 20.2 (±15.2) during the first 90-day period to 9.7 (±9.0) during the fourth 90-day period; the number of bleeding/spotting episodes decreased from 3.0 (±1.8) during the first 90-day period to 2.0 (±1.6). The two subgroups (previous placebo or previous DNG) differed, especially during the first 90-day period. The previous placebo group displayed a higher number of bleeding/ spotting days (24.5±16.4) and bleeding/spotting episodes (3.2±1.8) compared to previous DNG group (16.3±13.0 bleeding/spotting days and 2.8 ±1.8 bleeding/spotting episodes). Both groups had a reduction in numbers of bleeding/spotting days at end of the fourth 90-day period to 10.1±8.7 in the placebo group and 9.4±9.3 in the DNG group. Reduction in number of bleeding/spotting episodes was also observed after the fourth 90-day period to 2.1 ±1.6 in the placebo group and 1.9±1.5 in the previous DNG group.

The individual mean length of bleeding/spotting episodes reduced from 7.71 ±8.19 days during the first 90-day period to 4.83±2.52 during the fourth 90-day period. The patients from the previous placebo group experienced longer bleeding/spotting episodes (9.20±9.71 days) during the first 90-day period compared to these in the previous DNG group (6.21±6.02 days). Both groups displayed similar individual mean lengths of bleeding/spotting episodes during the fourth 90-day period, namely 4.85±2.53 in the previous placebo group compared to 4.81±2.54 in the previous DNG group.

Regarding the proportion of patients with improvement in intensity of bleeding during treatment with DNG, there was an observable trend toward reduction in frequency of patients describing heavy and normal intensity of bleeding and an increase in the frequency of patients reporting none or spotting only at the end of the fourth 90-day treatment period (Table 17**)**.

Table 17. Study A39700

Frequency of patients by maximal intensity of bleeding during 90-day Periods 1 and 4 – FAS

90-day reference period	Previous treatment: Placebo			Previous treatment: DNG 2 mg			TOTAL		
	N	Bleeding intensity	Number of patients (%)	N	Bleeding intensity	Number of patients (%)	N	Bleeding intensity	Number of patients (%)
1	79	None	1 (1.3)	85	None	8 (9.4)	164	None	9 (5.5)
		Spotting	7 (8.9)		Spotting	19 (22.4)		Spotting	26 (15.9)
		Light	28 (35.4)		Light	33 (38.8)		Light	61 (37.2)
		Normal	31 (39.2)		Normal	21 (24.7)		Normal	52 (31.7)
		Heavy	12 (15.2)		Heavy	4 (4.7)		Heavy	16 (9.8)
...	...			...			...		
4	66	None	14 (21.2)	70	None	18 (25.7)	136	None	32 (23.5)
		Spotting	17 (25.8)		Spotting	15 (21.4)		Spotting	32 (23.5)
		Light	27 (40.9)		Light	29 (41.4)		Light	56 (41.2)
		Normal	5 (7.6)		Normal	8 (11.4)		Normal	13 (9.6)
		Heavy	3 (4.5)		Heavy	0		Heavy	3 (2.2)

A summary of the bleeding data based on the 90-day reference period is shown in Table 18.

Table 18. Study A39700

Analysis of bleeding/spotting days and episodes, individual mean length, and bleeding intensity based on 90-day reference periods - FAS

90-day period	N	Number of bleeding/spotting days	N	Number of bleeding/spotting episodes	N	Individual mean length of bleeding/spotting episodes [days]
1	161	20.2 ± 15.2 [16.0]	160	3.0 ± 1.8 [3.0]	148	7.71 ± 8.19 [4.71]
2	157	13.5 ± 13.3 [11.0]	156	2.5 ± 2.0 [3.0]	119	5.58 ± 5.07 [4.75]
3	155	12.0 ± 12.4 [10.0]	154	2.3 ± 1.9 [3.0]	111	5.40 ± 5.89 [4.50]
4	132	9.7 ± 9.0 [9.0]	132	2.0 ± 1.6 [2.0]	98	4.83 ± 2.52 [4.33]

(Continued)

90-day reference Period 1			...	90-day reference Period 4		
N	Bleeding intensity	Number of patients (%)		N	Bleeding intensity	Number of patients (%)
164	None	9 (5.5)		136	None	32 (23.5)
	Spotting	26 (15.9)			Spotting	32 (23.5)
	Light	61 (37.2)			Light	56 (41.2)
	Normal	52 (31.7)			Normal	13 (9.6)
	Heavy	16 (9.8)			Heavy	3 (2.2)

Regarding the analysis of bleeding using the 28-day reference periods, the course of changes in the number of bleeding/ spotting episodes and days parallels that seen in the analysis by 90-day reference periods.

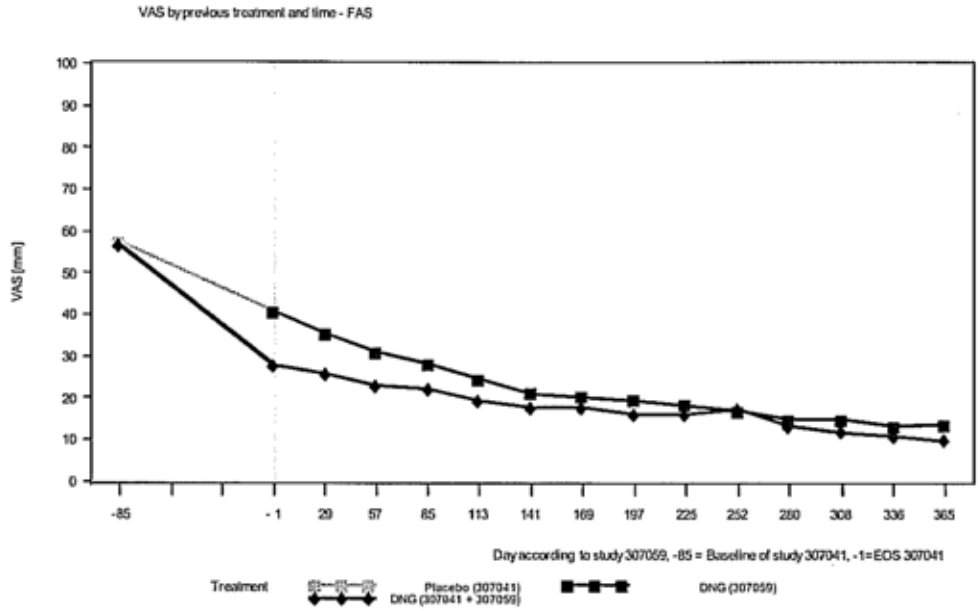
The results presented would indicate that the long-term use of Visanne is associated with a decreased frequency of bleeding/spotting days and episodes, decreased intensity of bleeding, shortened individual mean length of bleeding/spotting episodes and amenorrhoea in several cases.

Secondary Efficacy Outcomes

With regards to reduction in EAPP, baseline mean VAS for the total patient sample decreased throughout the study period, from a baseline of 34.08 mm (±21.60) to 17.69mm (±13.10) after 28 weeks and to 11.52mm (±11.26) after 52 weeks (EOT). In relation to the specific subgroups, in the previously placebo treated group, mean VAS dropped from 40.73mm (±21.14) at inclusion, to 19.48mm (±12.59) after 28 weeks and 13.49mm (±14.17) after 52 weeks (EOT). In the previously DNG treated group, there was a lower baseline value VAS of 27.89mm (±20.24), and this demonstrated continuous decrease to 16.14mm (± 13.41) at 28 weeks and 9.72mm (±7.43) at 52 weeks (Figure 5).

Figure 5.

TF 9: Graphic display [mean values] of EAPP assessment (VAS rating) during DNG treatment (by previous treatment in Study 307041) – FAS



It is reported that nearly 25% of patients did have to use some concomitant analgesia throughout the study. Onset of use of all concomitant medication was reported by 77 patients (45.8%). The more frequently used analgesics were ibuprofen in 19 patients (11.3%), paracetamol by 12 patients (7.1%), diclofenac by 10 patients (6.0%) and metamizole by 6 patients (3.6%).

Analgesics were predominantly used for EAPP although other reasons for use were also recorded for example, headache, back-pain. No further analysis of concomitant medication use was reported and there was no information provided as to whether there was an overall increase in amount of alternative analgesia required over the 12 month period. The evaluator would therefore interpret claims of continued reduction of EAPP whilst taking Visanne with some caution until further analysis of intake of rescue analgesia is provided.

Efficacy: Non-Pivotal Trials

Study A02266

This was a multi-centre, open, randomised phase 2 dose-finding study to assess the efficacy of Visanne (DNG 2mg) in comparison to 1mg and 4mg DNG. The study was conducted in accordance with GCP guidelines between October 1993 and January 1996. Women between menarche and menopause with laparoscopically confirmed endometriosis of r-AFS stages I, II and III were included. The r-AFS[xiv] staging of endometriosis is based on a points classification system at laparoscopy.

Exclusion criteria included endometriosis stage IV, significant comorbidities (for example, diabetes mellitus (DM) and thrombotic disease), and pregnancy. The primary target variables were laparoscopic control, classification of endometriosis according to r-AFS and clinical symptoms.

A total of 68 female patients were enrolled, and randomly allocated to various DNG dosage groups; 4 patients were in the 1mg group, 29 patients in the 2mg group and 35 patients in the 4mg group. The testing of the 1mg group was stopped due to lack of efficacy and increased bleeding events, hence only 4 patients were in this group. Patients were to take one tablet daily of study medication for a period of 24 weeks. Clinical measures such as symptoms of pain and bleeding patterns were assessed at baseline, 6, 12 and 24 Weeks (EOT). Laparoscopy was repeated at EOT. There were no significant differences in baseline demographics across the groups. With regard to stage of endometriosis as per r-AFS score, at baseline, the groups were comparable. In the 2mg DNG group, endometriosis was stage I for 10 patients (34.5%), stage II for 11 patients (37.9%) and stage III for 8 patients (27.6%). In the 4mg DNG group, stage I was present in 15 patients (42.9%), stage II for 12 patients (34.3%) and stage III for 8 patients (22.9%)

Fifty seven patients completed the study according to protocol. Five patients on the 2mg group prematurely discontinued the medication (3 due to AEs and 2 for other reasons), and 5 patients in the 4mg group dropped out (4 withdrew consent and 1 was withdrawn due to violation of inclusion and exclusion criteria). One patient in the 1mg group withdrew. After treatment there was no repeat laparoscopy performed in 2 of the patients in the 2mg group.

After 24 weeks there was a detectable shift toward lower endometriosis stages in both treatment groups. In the 2mg DNG group there was no endometriosis found in 5 patients (23.8%), 11 patients (52.4%) were classified as stage I, 2 patients (9.5%) stage II and 1 patient (4.8%) as stage III. In the 4mg DNG group there were 6 patients (20%) with no endometriosis, 15 patients (50%) classified with stage I, 8 patients (26.7%) with stage II and 1 patient (3.3%) with stage III.

This observed trend to reduction in endometriosis stage was also supported by statistical analysis of the mean number of points to evaluate the stage as per r-AFS score. For the 2mg DNG group, the mean score pre treatment was 11.4 (±9.2), and at EOT had reduced to 3.6 (±5.1) ($p<0.001$). In the 4mg group, the mean score was 9.7 (±7.9), and at EOT had reduced to 3.9 (±4.4) ($p<0.0001$).

Statistical comparison between the 2mg and 4mg groups revealed no differences between the groups.

Both dosages also showed reduction in clinical symptoms of endometriosis. Overall improvement in symptoms was seen in 45% of the 2mg group and 50% of the 4mg group. More specifically, dysmenorrhoea improved in 69.0% of patients treated with DNG 2mg and 54.3% of patients treated with DNG 4mg. For premenstrual pain, improvement was noted in 44.7% of the patients in the 2mg group and 37.1% in the 4mg group. Regarding dyspareunia, improvement was noted in 34.5% of the 2mg DNG group and 48.6% of the 4mg group. For diffuse pelvic pain, 27.6% of patients reported an improvement in the 2mg group compared to 54.3% in the 4mg group. There was no significant difference observed between the two dosage groups.

In this study of a small number of women, the data would support claims that Visanne treatment for 24 weeks reduces the severity of endometriotic lesions at laparoscopy with no significant differences between the 2mg and 4mg doses.

Study A01177

This was a phase 2 single centre, open-labelled uncontrolled study to investigate the efficacy of DNG 1mg twice daily with respect to reduction of endometriotic lesions as seen at laparoscopy. The study was performed in the pre-GCP era and reported in 1988, but was conducted in accordance with all applicable national regulations.

A total of 104 patients were enrolled in the study. They all had confirmed endometriosis (100 by laparoscopy, 4 by laparotomy), which was substantiated by histological examination and classified by EEC according to Semm. Overall, 46 patients were classified as stage 1, 40 stage II, 9 stage III and 9 stage IV. They took DNG 1mg twice daily for 24 weeks. However, according to the study protocol, during bleeding episodes, one group of patients was first administered an increased dose of 3mg, and a second group received only 1mg, and the remainder continued unchanged. Detail of numbers in these different groups and documentation of compliance measures were not provided.

At end of treatment, 100 patients consented to repeat laparoscopy. This revealed disappearance of evidence of active endometriosis in 65 patients (65%) (no endometriosis or scars only), partial remission in 20 patients (20%) and no change in 15 patients (15%).

Although total daily dose was the same, this study used a different dosage regimen to that proposed in the current application (DNG 1mg twice daily rather than DNG 2mg once daily). Also, certain groups of patients had prescribed dosage changes during bleeding episodes which are not accounted for in the analysis. Therefore, the evaluator feels that these data should be considered supportive at best, rather than direct evidence of the efficacy of Visanne.

Study A01176

This was a multi-centre, open-label, active controlled study to compare the effects of DNG 1mg twice daily to norethisterone acetate (NETA) 5mg twice daily over a 6 month period. The study was performed between 1983 and 1987, in the pre-GCP era. The trial was initially designed to be a three-way comparison between DNG, NETA and danazol, but the investigators were unable to obtain danazol from the sponsor or other source.

Women of childbearing age with endometriosis confirmed by laparoscopy and classified by the EEC according to Semm were enrolled and randomised using block randomisation to receive either DNG or NETA. A total of 119 patients were randomised to receive DNG 1mg twice daily and 48 patients were in the group which received NETA 5mg twice daily. Baseline demographics were comparable between the groups. In the DNG group, 61 patients were classified as stage I, 36 with stage II, 18 with stage III and 4 with stage IV. In the smaller NETA group, 32 cases were classified as stage I, 14 as stage II, 2 with stage III and none with stage IV. Enrolled patients were to take the study medication for 24 weeks. Clinical check ups were made at baseline, and Weeks 4, 12 and 24 of treatment, with patients being asked subjectively about other symptoms of endometriosis.

After 24 weeks, post treatment laparoscopy/ laparotomy results were available for 97 patients (81.5%) in the DNG group and 48 (100%) in the NETA treated group. The reasons stated for this is that “patients refused to have a second-look laparoscopy made or for other reasons were subject to clinical follow up only”. There was no information on compliance or premature discontinuation of treatment provided.

The treatment outcome judged by repeat laparoscopy revealed that 61 out of 97 patients (62.9%) that underwent second laparoscopy in the DNG group and 30 of 48 patients (62.5%) in the NETA

group had no active endometriosis lesions visible. A reduction in size and/ or number of lesions was reported in 25 patients (25.8%) in the DNG group and 11 patients (22.9%) in the NETA group. There was no change in endometriotic lesions demonstrated in 11 DNG patients (11.3%) and 7 patients (14.6%) in the NETA group.

This would imply that there is no significant difference in efficacy of DNG compared to NETA regarding reduction of endometriotic lesions. However, the evaluator feels that these results should be interpreted with some caution, with respect to the efficacy of the proposed drug Visanne. This study utilises a different dosing regimen to the proposed DNG 2mg once daily. Furthermore the analysis only included those patients who had a second laparoscopy, rather than all patients enrolled in the study. No account was made in the analysis for the drop-outs. In the DNG group, only 81.5% of the patients underwent a repeat laparoscopy, but in the NETA group 100% underwent the procedure, which potentially introduces bias in the descriptive analysis.

Summary of Efficacy

With regard to reduction of EAPP, Visanne was evaluated in a total of 222 women in two controlled trials with treatment duration of between 12 to 24 weeks. It is the opinion of the evaluator that Visanne was shown to be clinically and statistically significantly superior to placebo and also non-inferior to monthly injections of LA (a currently accepted treatment option). Despite relatively small numbers, the evaluator is of the opinion that the data supplied do provide adequate evidence of the efficacy of Visanne in the reduction of EAPP.

A further 168 women were evaluated for long term reduction in EAPP over a period of 12 months in a one-armed, uncontrolled extension study. The reduction in VAS for EAPP was maintained during this time. However, despite it being reported that approximately 25% of patients used some concomitant analgesia during the study, no further analysis of this is reported. There is no indication as to whether this represents an increase in rescue analgesia since treatment was commenced. Therefore, the evaluator is of the opinion that conclusions regarding long-term efficacy should be interpreted with caution and would seek clarification of this from the sponsor.

Regarding reduction of lesions seen at laparoscopy, Visanne was evaluated in only 29 women, in the formulation of dienogest 2mg once daily. In this small study, a trend was seen to reduction in the stage of endometriosis as per r-AFS criteria, which were supported by statistically significant reduction in the total number of points accumulated using this score. No difference was observed between Visanne and a higher dose of DNG 4mg once daily.

Data was also presented regarding the efficacy of dienogest 1mg twice daily for a further 223 patients from two earlier pre-GCP studies. While on initial inspection, the results appear encouraging, lack of accounting for compliance, dosage changes and study drop-outs, coupled with the fact that the studies utilise a different dosage regimen, would lead the evaluator to treat this data with caution in drawing conclusions as to the efficacy of Visanne.

Efficacy Conclusions

- *Visanne was shown to be superior to placebo in reduction of EAPP as assessed by change in VAS (A32473). There was a mean decrease of 28.8mm with Visanne compared to 16.9mm for placebo.*
- *Visanne demonstrated equivalence to a standard treatment (injection of LA every 4 weeks) in reduction of EAPP as assessed by change in VAS (AU19). The mean decrease was 47.5mm for Visanne compared to 46.0mm for LA.*
- *In a small number of women (n=29) Visanne, reduced the severity of endometriosis found at laparoscopy after treatment as assessed using the r-AFS (A02266).*

- *During a 12 month open-label extension with Visanne 2mg (A39700) daily, VAS scores for EAPP remained low and continued to improve. However, approximately 25% of patients used some other analgesia on occasion and the amounts used specifically for endometriosis-related pain need to be clarified before conclusions regarding long-term efficacy can be drawn.*

Safety

Nine clinical phase 2/3 studies involving 724 women provided data on the safety of Visanne. Six were the phase 2/3 studies described above to demonstrate efficacy of Visanne in reduction of EAPP or the reduction in severity of endometriotic lesions. Three other studies were included for completeness (B567, A04431 and A05436), but these utilised different doses of DNG or different dosage regimens or different study populations, and thus do not match the marketing application for Visanne.

Therefore safety data from the pivotal studies A32473 and AU19, together with the extension study A39700 and study A02266 have been evaluated as they were considered relevant to the clinical safety assessment of Visanne. They were considered comparable with regards to data collection and representative of the target population, and the sponsor submitted a pooled evaluation utilising these studies.

The pre-GCP studies A01177 and A01176 and studies B567, A04431 and A05436 have been summarised in this safety evaluation as supportive data because different standards of safety evaluation were applicable at the time these studies were performed.

Pivotal Studies

Study A32473

Drug Exposure

A total of 102 patients were randomised to the DNG group and received at least one dose. These were compared with 96 patients who received placebo. The total planned exposure for patients receiving DNG was 2mg once daily for 84 days, a planned total of 168mg DNG during the study period.

Details of any AE (observed, volunteered or elicited) were documented, including onset, duration, intensity, likely relationship to study drug and outcome. Assessment of seriousness of the AE was made by the investigator and was to be reported immediately. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Bleeding events were recorded in patient diaries. Laboratory tests were done at screening and EOT, physical examination was conducted at screening and EOT.

Overview of Adverse Events

A total of 122 AEs were reported in the study, 51 in the placebo group (affecting 25 patients in this group or 26%) and 71 in the DNG group (affecting 34 patients or 33.3%).

The most frequent AEs (≥2.0% of patients) in the DNG group were: headache (10.8%); cystitis (2.9%); nausea (2.9%); and nasopharyngitis, bronchitis, influenza, depression, breast discomfort, and asthenia (each 2.0%). For the placebo group, the most frequent AEs were: headache (5.2%); nasopharyngitis (5.2%); bronchitis, influenza, and vomiting (each 3.1%); and depression, gastritis, proteinuria, and vaginal candidiasis (each 2.1%) (Table 19**)**.

Table 19. Study A32473

Display of most frequent AEs (at least 2% of FAS) – FAS

MedDRA Preferred Term (Version 10.0)	Placebo (n = 96)			DNG (n = 102)		
	Events	No. of pat.	% of pat.	Events	No. of pat.	% of pat.
ANY EVENTS	51	25	26.0	71	34	33.3
Headache	6	5	5.2	18	11	10.8
Cystitis	-	-	-	3	3	2.9
Nausea	1	1	1.0	3	3	2.9
Nasopharyngitis	6	5	5.2	2	2	2.0
Bronchitis	3	3	3.1	2	2	2.0
Influenza	3	3	3.1	2	2	2.0
Depression	2	2	2.1	2	2	2.0
Breast discomfort	1	1	1.0	2	2	2.0
Asthenia	-	-	-	2	2	2.0
Vomiting	3	3	3.1	-	-	-
Gastritis	2	2	2.1	-	-	-
Proteinuria	2	2	2.1	-	-	-
Vaginal candidiasis	2	2	2.1	-	-	-

Source: T 128 and T 130. The order of presentation is based on the frequency of ***patients*** in the DNG group. The sign "-" replaces "0 (0.0%)" for clarity.

A total of 43 adverse drug reactions (ADRs; or AEs at least possibly related to the study medication) were reported. In general the frequency of patients with ADRs in the DNG group was 14.7%, which was higher than that for placebo 7.3%. The most frequent ADRs for DNG were: headache (2.9%); breast discomfort, nausea, asthenia, and depression (each in 2.0% of the FAS). The most frequent ADR for placebo was headache (3.1%). Other ADRs were single cases (Table 20**).**

Table 20. Study A32473

Display of most frequent ADRs (at least 2% of FAS) – FAS

MedDRA Preferred Term (Version 10.0)	Placebo (n = 96)			DNG (n = 102)		
	Events	No. of pat.	% of pat.	Events	No. of pat.	% of pat.
ANY ADRs	10	7	7.3	33	15	14.7
Headache	4	3	3.1	8	3	2.9
Breast discomfort	1	1	1.0	2	2	2.0
Nausea	1	1	1.0	2	2	2.0
Asthenia	-	-	-	2	2	2.0
Depression	-	-	-	2	2	2.0

Source: T 146 and T 157. ADR = Adverse drug reaction (AE at least possibly related to study drug). The order of presentation is based on the frequency of ***patients*** in the DNG group. The sign "-" replaces "0 (0.0%)" for clarity. Note that the cases do not sum up to the totals (only most frequent ADRs of DNG were selected).

AEs of mild intensity were more frequent among the DNG patients (17.6%) than among placebo (8.3%), and AEs of severe intensity were more frequent under placebo (5.2%) compared to DNG (1.0%).

Serious Adverse Events, Deaths and Discontinuations due to Adverse Events

There were no deaths or serious AEs during the study. Premature discontinuation of study medication due to AEs occurred in three patients. One patient withdrew in the placebo group (1%) due to elevation of blood human chorionic gonadotrophin (HCG; event probably unrelated). In the DNG group, two patients withdrew (2%). One patient began to complain of breast pain eleven days into taking the study medication, and persisted for a further 4 weeks before discontinuing; this was considered probably related to the study medication. Another patient experienced uterine bleeding which commenced 23 days after starting the study medication, and persisted for 17 days. DNG was discontinued 2 days later. This was considered possibly related to the study medication.

Adverse Events of Special Interest

AEs of gynaecological interest are summarised in Table 21**)**. Breast symptoms were more common in the DNG group (4 patients) compared to placebo (2 patients). Gynaecological infections were seen in both groups (3 cases in DNG group; 2 with placebo). There were two cases of elevated HCG (one in each group, and both unrelated to pregnancy).

Table 21. Study A32473

Display of AEs of gynecological interest – FAS

MedDRA SOC / Preferred Term (PT) (Version 10.0)	Placebo (n = 96)			DNG (n = 102)		
	Events	No. of pat.	% of pat.	Events	No. of pat.	% of pat.
Reproductive system and breast TOTAL	4	4	4.2	7	7	6.9
Breast discomfort	1	1	1.0	2	2	2.0
Breast engorgement	-	-	-	1	1	1.0
Breast pain	1	1	1.0	1	1	1.0
Fibrocystic breast disease	-	-	-	1	1	1.0
Ovarian cyst	1	1	1.0	1	1	1.0
Uterine haemorrhage	-	-	-	1	1	1.0
Vaginal discharge	1	1	1.0	-	-	-
Infections and infestations TOTAL*	19	15	15.6	15	11	10.8
Vaginal candidiasis	2	2	2.1	-	-	-
Vaginal infection	-	-	-	1	1	1.0
Vaginitis bacterial	-	-	-	1	1	1.0
Vulvovaginitis	-	-	-	1	1	1.0
Investigations TOTAL*	2	2	2.1	6	5	4.9
Blood human chorionic gonadotropin increased	1	1	1.0	1	1	1.0

Source: T 128. SOC = System Organ Classification. * Only events of gynecological interest were selected, therefore the sum of the PTs does not add to TOTAL of each SOC. The sign "-" replaces "0 (0.0%)" for clarity.

It was noted that headaches was more frequent in patients treated with DNG (10.8%) compared to placebo (5.2%) whereas depression was observed in 2 patients in each group.

Regarding uterine bleeding patterns, the DNG group were treated with continuous progestogen, compared with the placebo group under no exogenous hormonal influence. As expected, the placebo group documented bleeding patterns consistent with regular menses, and the DNG group was characterised by relatively de-synchronised bleeding of relatively mild intensity.

At EOT, there were no abnormal cervical smears in either group.

Laboratory Abnormalities, Vital Signs and Physical Examination

Laboratory measurements included haematology, biochemistry, and urinalysis. The mean values for all laboratory parameters were normal at screening and remained normal at EOT. Individual clinically significant abnormalities from both groups were documented; the only events considered possibly related to DNG were the increases of gamma glutamyl transpeptidase (GGT) and alanine-aminotransferase (ALT) in the same patient.

Oestradiol levels were checked and the mean levels were 0.273nmol/L (±0.244) for the DNG group and 0.247nmol/L (±0.325) for placebo at screening. At EOT, the mean levels were lower in the DNG group (0.203 ±0.199nmol/L) compared to the placebo group (0.505 ±1.749nmol/L). The decrease in the DNG group would be compatible with modest oestradiol suppression. The increase in the placebo group may reflect normal cyclical changes.

Regarding physical examination, vital signs were comparable and stable in both groups. Hypertension (blood pressure (BP) >140/90) was documented in 2 patients in the placebo group and one in the DNG group. There were no significant abnormal changes in physical examination in either group.

Study AU19

Drug Exposure

A total of 120 women were randomised to receive DNG 2mg once daily for 24 weeks, a total cumulative dose of 336mg DNG. Due to compliance, the mean exposure to DNG was 330.6mg (range 56 to 392mg). There were 128 women randomised to receive IM injections of LA 3.75mg every four weeks for 24 weeks; a total of six injections giving a cumulative maximum dose of 22.5mg. Only 118 women received all six injections as per protocol, giving a mean exposure of 21.4mg (range 3.75 to 22.5mg).

In general, adverse events were only recorded if spontaneously reported by the patients. However, certain adverse events were expected to occur under the treatments given and the more frequent of these were assessed by direct questioning. For DNG, these included: irregular bleeding, hot flushes, breast pain, nausea, vomiting, bloating, headache and depressed moods. For LA these included: hot flushes, sweating, mood instability, loss of libido, vaginal dryness, breast symptoms, headaches and arthralgias. The patients were required to document episodes of bleeding and hot flushes specifically on their diary card.

Physical examination and laboratory assessments were performed at baseline and EOT, along with vital signs and adverse event questioning which was also performed at week 12.

A subgroup of patients from three of the study centres had their BMD measured by Dual energy x-ray absorptiometry (DEXA) scanning at baseline and EOT for analysis of the potential effects of the treatments on bone mineralisation.

With regard to the data presented in the report regarding safety, the evaluator has concentrated predominantly on those reported in the FAS.

Overview of Adverse Events

During treatment, there were 380 events in 82 women (68.3%) of the DNG group and 408 events in 95 women (74.2%) of the LA group. The most frequently observed AEs in the DNG group were headache (20.8%), flu syndrome (10.0%), abdominal pain (9.2%), weight gain (7.5%) and depression (6.7%). In the LA group, the most frequently observed AEs were headache (32%), depression (10.2%), sleep disorder (9.4%), back pain (8.6%), nausea (7.8%), hot flushes (7.0%),

decreased libido (7.0%), vaginal dryness (7.0%) and upper respiratory tract infection (7.0%) (Table 22**)**.

Table 22. Study AU19

Frequency of AEs and percentage of women afflicted with AEs (at least 5% in either treatment group) during treatment period - FAS

	DNG group (n=120)		LA group (n=128)	
HARTS CODE	events	women with AE n (%)	events	women with AE n (%)
Any event	380	82 (68.3%)	408	**95 (74.2%)**
Headache	48	25 (20.8%)	63	**41 (32.0%)**
Flue syndrome	15	**12 (10.0%)**	12	8 (6.3%)
Abdominal pain	19	**11 (9.2%)**	4	4 (3.1%)
Weight gain	14	**9 (7.5%)**	7	5 (3.9%)
Depression	10	8 (6.7%)	19	**13 (10.2%)**
Back pain	7	7 (5.8%)	13	**11 (8.6%)**
Nausea	8	7 (5.8%)	10	**10 (7.8%)**
Pelvic pain	21	**7 (5.8%)**	7	6 (4.7%)
Upper respiratory infection	7	6 (5.0%)	11	**9 (7.0%)**
Alopecia	11	6 (5.0%)	10	**7 (5.5%)**
Acne	8	5 (4.2%)	9	**7 (5.5%)**
Decreased libido	10	5 (4.2%)	15	**9 (7.0%)**
Vaginal dryness	5	3 (2.5%)	14	**9 (7.0%)**
Migraine	5	3 (2.5%)	11	**8 (6.3%)**
Sleep disorder	2	2 (1.7%)	18	**12 (9.4%)**
Hot flushes	2	1 (0.8%)	16	**9 (7.0%)**

bold = indicates group with more frequent occurrence of respective event

A total of 10.8% of women in the DNG group and 10.9% in the LA group described their AEs as mild intensity; 40.0% of women in the DNG group and 46.1 in the LA group had AEs of moderate intensity, and 14.2% of women in the DNG group and 16.4% in the LA group had AEs of severe intensity.

The investigators assessed the relationship of the reported AEs to the study drug. A total of 41.6% of the women in the DNG group and 47.7% in the LA group were assessed as having an AE which was at least possibly treatment related (assessed as definite, probable or possible). The most frequent for the DNG group were headache (12.5%), weight gain (6.7%), depression (5.0%), and decreased libido (4.2%). In the LA group, the most frequent possible ADRs were headache (19.5%), depression (8.6%), sleep disorder (7.8%), vaginal dryness (7.0%), hot flushes (7.0%), decreased libido (6.3%), and alopecia (5.5%) (Table 23**)**.

Table 23. Study AU19

Number and percentage of women with at least possibly treatment related AEs (in ≥4% of the women in either treatment group)

HARTS CODE	DNG group (n=120) women with at least possibly related AE		LA group (n=128) women with at least possibly related AE	
	n	(%)	n	(%)
ANY EVENT	50	41.6	61	47.7
Headache	15	12.5	25	**19.5**
Weight gain	8	**6.7**	5	3.9
Depression	6	5.0	11	**8.6**
Decreased libido	5	4.2	8	**6.3**
Acne	5	4.1	6	**4.7**
Alopecia	4	3.3	7	**5.5**
Migraine	3	2.5	6	**4.7**
Sleep disorder	2	1.7	10	**7.8**
Vaginal dryness	2	1.7	9	**7.0**
Hot flushes	0	0.0	9	**7.0**

bold = indicates group with more frequent occurrence of respective event

Serious Adverse Events, Deaths and Discontinuations due to Adverse Events

There were no deaths during the study.

There were 7 serious AEs reported, 6 events for 5 patients in the DNG group and one in the LA group. In the DNG group, one patient suffered a severe depression. Furthermore, one patient underwent hysterectomy, one was hospitalised for abdominal pain, one for pelvic pain and one patient underwent two hospital admissions for a renal calculus. In the LA group, one patient suffered a disc prolapse requiring hospitalisation. With the exception of the patient with depression, these AEs were considered unlikely due to the study medication. Depression was considered "possibly" related because mood changes have been previously described under sex hormone treatment and the patient developed the symptoms after taking DNG for 3.5 months.

A total of 5.0% of the women in the DNG group (6/120) and 3.9% of women in the LA group (5/128) discontinued study medication prematurely due to adverse events. In the DNG group, the AEs leading to premature discontinuation were hypertension, tinnitus, ovarian cyst, nausea and depression. In the LA group, these were hot flushes, arthritis, depression, allergic reaction and sleep disorder.

Adverse Events of Special Interest

Special attention was paid to recording and analysis of bleeding patterns and incidence of hot flushes. Bleeding data were obtained from the patient dairies and analysed by 90-day reference periods as per WHO recommendations, with the first reference period starting on the first day of the study medication. In general, the number of bleeding/spotting episodes decreased in both treatment groups and a higher incidence of bleeding/spotting was observed in the DNG group compared to LA. The results of the FAS and PPS were similar.

In the FAS, the mean number of bleeding/ spotting episodes in the DNG group decreased from 3.33 in reference period 1 to 1.87 episodes in reference period 2. In the LA group, the mean decreased from 2.02 in period 1 to 0.47 in period 2 (Table 24). The number of bleeding/spotting days decreased in both groups. In the DNG group, the mean number of bleeding/spotting days decreased from 25.6 in reference period 1 to 11.8 in period 2. In the LA group, the mean number of

bleeding/spotting days decreased from 11.6 in period 1 to 2.0 bleeding/spotting days in period 2 (Table 25). Furthermore, the number of "spotting only" days decreased in both groups.

Table 24. Study AU19

Number of bleeding/spotting episodes (FAS)

Reference period	DNG group			LA group		
	n	mean	SD	n	mean	SD
1	110	3.33	1.82	115	2.02	1.20
2	101	1.87	2.01	113	0.47	1.13

Table 25. Study AU19

Number of bleeding/spotting days (FAS)

Reference period	DNG group			LA group		
	n	mean	SD	n	mean	SD
1	110	25.61	18.50	115	11.61	7.01
2	104	11.81	15.10	114	2.00	4.90

The number of days and intensity of hot flushes was analysed from the patient diaries. Again, results for the FAS and PPS were similar, and the FAS is reported in this evaluation. Overall, during the entire study the women in the DNG group had fewer days with hot flushes compared to the women in the LA group. In the DNG group, the mean number of days with hot flushes per week decreased from 1.04 days in week 1 to 0.82 days in week 24, whereas in the LA group, the mean number of days with hot flushes per week increased from 0.78 days in week 1 to 4.70 days in week 24 (Table 26).

Table 26. Study AU19

Mean number of days with hot flushes per week during entire study (FAS and PP)

Analysis Set	DNG group			LA group		
	n *	mean	SD	n	mean	SD
PP	2167	0.8370	1.8909	2268	4.1267	3.0170
FAS	2712	0.8918	1.9490	2946	4.2319	3.0171

*: The column 'n' represents the overall number of treatment weeks summarizing all women, i.e. for one single woman there could be up to 24 observations. A treatment week was only included if observations of hot flushes for at least 4 days in this week were available. For these weeks, missing data were replaced with the average number of hot flushes for the days where data were available.

In the DNG group, 36 women reported flushes in Week 1 that were rated as mild in 50.0%, moderate in 41.7% and severe in 8.3%. In Week 24, 19 women reported hot flushes that were mild in 47.4%, moderate in 31.6% and severe in 21.1%. In the LA group, 41 women reported flushes in Week 1 that were rated as mild in 63.4%, moderate in 31.7% and severe in 4.9%. In Week 24, 83 women reported hot flushes that were mild in 33.7%, moderate in 37.3% and severe in 28.9%.

The number of women affected by hot flushes and the number of days per week that they were experienced appeared to decrease over time on treatment with DNG whereas, in the LA group, the incidence of hot flushes appears to increase.

Bone mineral density analysis

The BMD of the lumbar spine (L1-L4) was measured at screening and EOT by Dual energy x-ray absorptiometry (DEXA) scanning in a subgroup across three centres. Patients with a BMD >2.5 SD below standard were excluded. Sample size calculations are presented that suggest that, allowing for drop-outs, there needed to be 32 patients in each treatment group, that is, a total of 64 patients included. In the FAS, 26 women were in the DNG group and 31 in the LA group, and the PPS had only 19 patients in the DNG group and 23 in the LA group, so the sample can be seen to be small.

In the FAS group at screening, mean density at the lumbar spine was 1.0616g/cm^2 in the DNG group (n=26) and 1.0704g/cm^2 in the LA group (n=31). At EOT, mean density was 1.0362g/cm^2 in the DNG group (n=23) and 1.0135g/cm^2 in the LA group (n=30). This would represent an overall change in the mean of -0.0254g/cm^2 for the DNG group and -0.0569g/cm^2 in the LA group.

However, the report then states that for women with measurements available at both screening and final visit, this amounted to an absolute mean change of +0.0022g/cm^2 in the DNG group (n=21) and of -0.0415g/cm^2 in the LA group (n=29). This raises the question to the evaluator regarding the DNG group that the omission in the analysis of patients who had variables missing alters the mean individual change in BMD from a negative value (-0.0254g/cm^2) to a positive value (+0.0022g/cm^2). This could be explained by patients with baseline values but no EOT measurements being outliers at the higher end of the BMD value spectrum on initial testing. The evaluator feels that more explanation for the drop-out of these patients should be provided in the report.

The ensuing statistical analysis regarding mean individual percentage change in BMD, is presumably then based on those patients with both baseline and EOT values available, and demonstrated that the hypothesis of having a higher reduction of BMD under treatment with DNG than LA could be rejected. It is also concluded that the difference between the treatment groups was 4.29% in the FAS (95% CI 1.93, 6.66) which is statistically significant.

However the evaluator considers that this has not been adequately demonstrated, with numbers being small and some discrepancies evident between the effects of DNG on mean BMD according to the population analysed.

Laboratory Abnormalities and Vital Signs and Physical Examination

Laboratory parameters measured included haematology, biochemistry, urinalysis, and in the BMD analysis subgroup, specific bone metabolism parameters were checked. There were no pronounced differences between the groups regarding routine haematology and biochemistry. There were no clinically significant changes in these parameters over time in either group.

With regard to levels of the hormones oestradiol and FSH, they decreased from baseline to EOT in both groups, with a marked decrease in mean oestradiol in the LA group from 299.0 pmol/L (±171.7) to 68.5 pmol/L (±95.1). In the DNG group, this reduction was not as marked, with mean oestradiol levels 256.3pmol/L (±161.2) at baseline, falling to 249.9pmol/L (±374.4) at EOT.

Regarding the specific laboratory bone markers that were analysed in the BMD subgroup, serum concentrations of osteocalcin and bone alkaline phosphatise, as well as urinary CrossLaps and calcium were measured at baseline and EOT. There were a total of 30 women in the DNG group and 32 in the LA group. Osteocalcin is a parameter for bone formation, and the mean value slightly decreased in the DNG group and increased in the LA group. Bone specific alkaline phosphatase is a parameter for osteoblast differentiation. The mean concentration increased in the DNG group from 10.1 µg/L (±4.2) to 10.3 (±3.5). There was more marked increase in the LA group from 10.6 µg/L (±3.8) at baseline to 13.9 µg/L (±4.0) at EOT. Urine CrossLaps are a parameter for bone

resorption[4]. In the DNG group, the mean concentration increased slightly, whereas in the LA group, there was a marked increase after 24 weeks of treatment. Urinary calcium can be used as a parameter for bone resorption and in the DNG group the mean calcium concentration had decreased from 388.6 (±244.4) mmol/mol creatinine to 266.5 (± 160.0) after 24 weeks of treatment. In the LA group, the trend was reversed, rising from 285.6 (±172.7) to 403.6 (±195.6) mmol/mol creatinine. These results would suggest an increase of bone resorption in the LA group compared to the DNG group.

There were minimal changes in heart rate or blood pressure from baseline to EOT in both groups, which were not significant, and there was no relevant difference between the groups. There was a mean increase in weight of 1.21kg in the DNG group and 1.15kg in the LA group. There were 8 women in each treatment group that had a change recorded in physical examination findings at EOT, none of which were considered related to the study medication.

Safety: Extension Studies

Study A39700

Drug Exposure

A total of 168 patients who completed study A32473 were included in this one-arm follow up and received at least one dose of study medication. In the preceding study, 87 patients had been treated with DNG, and 81 had received placebo – making this study their first exposure to DNG. The expected total exposure to DNG during the planned study period of 52 weeks was 728mg.

At each visit after the start of treatment, patients were given the opportunity to report AEs. Complaints had to be spontaneously volunteered rather than directly elicited. Any AEs were documented, including onset, seriousness, duration, intensity and likely relationship to the study drug. Adverse events were rated as serious if they were fatal or life-threatening, resulted in persistent disability or required in-patient hospitalisation. Blood tests, urinalysis, assessment of vital signs and gynaecological examination were performed regularly throughout the study period. Full physical examination and cervical smear were performed at baseline and end of trial.

Due to this study being a follow on study, AEs that had started during the precious study were analysed separately as ongoing from A32473.

Summary of Ongoing Adverse Events from Study A32473

There were 24 AEs which did not recover during study A32473, affecting 15 from 168 patients (8.9%) included in this study. None of these was considered a serious AE and none led to premature discontinuation of the study medication during this study.

The relationship to the study drug was assessed as definite for 1 AE (Breast discomfort). A possible relationship was considered for 9 AEs in 6 patients (3.6%) as follows: flatulence, asthenia, ALAT increased, GGT increased, depression in 2 patients, fibrocystic breast disease, ovarian cyst and photosensitivity reaction. All other ongoing AEs were assessed as unlikely or not related to the study drug.

[4] Urinary CrossLaps, determined by ELISA adjusted for urinary creatinine, has been shown to be a sensitive and specific marker of bone resorption, because it measures a C-terminal telopeptide (8 amino acids) of the α-1 chain of type 1 collagen. ELISA= Enzyme-Linked Immuno-Sorbent Assay.

Overview of Adverse Events

There were 171 AEs reported during the treatment phase in 76 of all 168 patients (45.2%), with 3 rated as serious and 4 leading to premature discontinuation, which are discussed in more detail below.

The most frequent AEs were Headache (16 AEs in 14 patients, 8.3%), Nasopharyngitis (17 AEs in 14 patients, 8.3%), Breast discomfort (13 AEs in 12 patients, 7.1%), and Nausea (8 AEs in 8 patients, 4.8%). Other AEs occurred in less than 5 patients (Table 27**)**. The majority of the AEs (85 out of 171) were rated as mild intensity, with 9 rated as severe intensity. The main pattern of the AEs was continuous in 138 of 171 events.

With regard to relationship to the study drug, 40 AEs in 27 patients (16.1%) were classified as possibly related (38 AEs) or probably related (2 AEs), and have thus been considered as ADRs. The most frequent ADRs were breast discomfort (8 AEs in 7 patients, 4.2%), nausea (5 AEs in 5 patients, 3.0%), and irritability (5 AEs in 4 patients, 2.4%) (Table 28**)**. Further ADRs were as follows: abdominal pain, gastrointestinal inflammation, fatigue, weight increased, headache, migraine, depressed mood, depression, sleep disorder, breast engorgement, breast induration, breast mass, menorrhagia, haemorrhagic ovarian cyst, ovarian cyst, dry skin, and hot flush.

Table 27. Study A39700

Display of most frequent AEs (in > 2% of FAS) – FAS

MedDRA Preferred Term (Version 10.0)	DNG (N = 168)		
	Events	No. of pat.	% of pat.
ANY EVENTS	51	25	26.0
Headache	16	14	8.3
Nasopharyngitis	17	14	8.3
Breast discomfort	13	12	7.1
Nausea	8	8	4.8
Irritability	5	4	2.4
Bronchitis	5	4	2.4
Influenza	4	4	2.4
Leukocyturia	5	4	2.4
Proteinuria	4	4	2.4
Ovarian cyst	4	4	2.4

Source: T 66.

Table 28. Study A39700

Display of most frequent ADRs (in > 1% of FAS) – FAS

MedDRA Preferred Term (Version 10.0)	DNG (N = 168)		
	Events	No. of pat.	% of pat.
ANY ADRs	40	27	16.1
Breast discomfort	8	7	4.2
Nausea	5	5	3.0
Irritability	5	4	2.4
Breast engorgement	3	3	1.8
Headache	3	2	1.2

Source: T 86 and T 88.

Deaths, Serious Adverse Events and Discontinuations due to Adverse Events

There were no deaths during the study.

There were 3 AEs in 3 patients (1.8%) during treatment which were rated as serious, and one patient experienced one SAE after the end of the study period. One patient was diagnosed with cholelithiasis during treatment with the study medication, and required admission to hospital for laparoscopic cholecystectomy. This event was considered by the investigators unlikely to be related to the study medication and there was no change in her dosing regimen. One patient complained of depression, and required brief psychiatric admission. She withdrew her consent for the study as a result of this. The investigator felt that this was probably related to the study medication. One patient with a history of recurrent sinusitis at screening developed worsening of her chronic sinusitis, requiring admission to hospital and nasal surgery. She was recovering from this at the end of the trial. It was felt by the investigators that this was unlikely related to the study medication. One patient, who prematurely discontinued the study medication for worsening migraine, presented three months later with a mass in her upper right breast. This was diagnosed as invasive ductal carcinoma, and she underwent radical mastectomy. The tumour was not hormone sensitive on pathological analysis, thus the investigator changed her initial assessment of causality of this SAE from possible to unlikely related to the study medication.

During the treatment phase, 4 AEs in 4 patients led to the premature discontinuation of the study medication. One patient with depression is described in the SAEs above. One patient, with a history of migraine, developed recurrent episodes of migraine (1-2 per month) after starting treatment. The study medication was withdrawn after 174 days. It was considered by the investigator that this was possibly related to the study medication. Of note, this is the same patient who developed breast cancer as described above. One patient gained 5kg after taking DNG for a total of 196 days (84 in study A32473 and 112days in present study) and the drug was withdrawn. The investigators felt that this was unrelated to the study medication. Another patient reported breast pain of moderate intensity after 9 days of taking the study medication. In study A32473, she had received placebo, so this represented her first exposure to DNG. The AE was assessed as possibly related to DNG, and she persevered with the study for another month before DNG was withdrawn. Her symptoms abated on cessation of the drug.

Adverse Events of Special Interest

Regarding treatment with sex hormones, AEs of gynaecological interest and also those pertaining to vascular disorders, nervous system disorders and psychiatric complaints are of particular interest.

Regarding gynaecological AEs, these are summarised in Table 29. Overall there were 30 events in 26 patients related to Reproductive system and breast. There were 13 episodes in 12 patients (7.1%) of breast discomfort. ovarian cysts occurred on 4 occasions in 4 patients (2.4%). There were a total of 14 episodes of Gynaecological infection reported.

There were 16 episodes of headache reported in 14 patients (8.3%). Psychiatric complaints were reported in 5 patients (3.0%), with 3 episodes of depression. Regarding vascular AEs, only 2 were reported, one of hypertension and one of hot flush.

Table 29. Study A39700

Display of AEs of gynecological interest – FAS

MedDRA SOC / Preferred Term (PT) (Version 10.0)	DNG (N = 168)		
	Events	No. of pat.	% of pat.
Reproductive system and breast TOTAL	30	26	15.5
Breast discomfort	13	12	7.1
Ovarian cyst	4	4	2.4
Breast engorgement	3	3	1.8
Breast induration	1	1	0.6
Breast mass	1	1	0.6
Breast pain	1	1	0.6
Haemorrhagic ovarian cyst	1	1	0.6
Menorrhagia	1	1	0.6
Metrorrhagia	1	1	0.6
Pelvic pain	1	1	0.6
Polymenorrhoea	1	1	0.6
Vaginal discharge	1	1	0.6
Vulvovaginal pruritus	1	1	0.6
AEs with onset after end of treatment phase (see Listing in T 93)*:			
Cervical dysplasia	2	2	1.2
Breast cancer	1	1	0.6
Breast mass	1	1	0.6
Infections and infestations TOTAL**	53	41	24.4
Infections of gynecological interest:			
Vaginal candidiasis	3	3	1.8
Vulvovaginal mycotic infection	4	3	1.8
Vulvovaginitis	3	3	1.8
Genital herpes	2	2	1.2
Urogenital infection fungal	1	1	0.6
Vaginal infection	1	1	0.6

Source: T 66.
LEGEND: SOC = System Organ Classification; *) Frequencies and percentages added by medical writer (see also Sections 9.7.1.8.3 and 12.2.1.3); **) Only events of gynecological interest were selected, therefore the sum of the PTs does not add to TOTAL of each SOC.

Laboratory Abnormalities, Vital Signs and Physical Examination

Laboratory parameters measured included haematology, biochemistry, oestradiol measurement and urinalysis. Mean values of all parameters were within normal limits at baseline and there was

negligible mean absolute changes at EOT. Regarding individual clinically significant laboratory abnormalities, these were identified by means of pre-determined alert ranges outside of normal limits. There was one case which was considered to be clinically significant and possible related to DNG, which was one patient with raised ALT and GGT. This was the same patient with theses laboratory abnormalities from study A32473.

Mean oestradiol levels ranged between 0.216 ±0.232 and 0.289 ±0.284nmol/L throughput the time measurement points. There was high variability of values between patients.

Mean blood pressure levels were normal and stable throughout the study. Individual episodes of elevated blood pressure (>140/90mmHg) were documented in 4 cases, and in two of these it was considered to be an AE. There were no abnormalities of heart rate noted. There were two patients with abnormal cervical smears at EOT, both showing cervical dysplasia, and neither considered to be likely related to DNG.

Safety: Non-pivotal Studies

Study A02266

A total of 68 patients received DNG in this study, and were randomised to three dosage groups. Four women received 1mg daily, 29 patients received 2mg daily and 35 received 4mg daily. The patients took the study medication every day for 24 weeks. One patient in the 1mg group, 5 patients in the 2mg group and 5 patients in the 4mg group dropped out.

During the study adverse events were recorded in 80.88% of all patients. The incidence of AEs was 50%, 75.9% and 88.6% in the 1mg, 2mg and 4mg groups, respectively. There were 171 AEs in total for the 2mg group and 188 for the 4mg group.

The most frequent adverse events were acne (in 32.2%), hot flushes (23.5%), abdominal pain (13.2%), breast pain (13.2%) and hypertrichosis (10.3%). According to the investigators, most of the adverse events were at least possibly related to the medication. Breaking the AEs down by dosage, there were more AEs in the 4mg group than in the 2mg group. The most frequent AEs in the 2mg group were acne (37.9%), headache (34.5%), flatulence (27.6%), depressed mood (24.1%) and hot flushes (24.1%). For the 4mg group, the most frequently reported were headache (47.1%), flatulence (38.2%), acne (29.4%), abdominal distension (26.5%), hot flushes (20.6%) depressed mood (17.6%) and vomiting (14.7%).

The majority of these adverse events were rated as “mild” or “clearly seen”. There were 14 AEs in the 2mg group classified as severe, with 3 cases each of lower abdominal and back pain, and two cases of acne. In the 4mg group, there were 8 severe AEs experienced, with alopecia in 4 cases, hot flushes in 2 cases and one each of breast pain and acne.

There were no deaths during the study. There were two adverse events judged as serious; both were cases of ovarian cyst. One of these cases was judged as possibly related to the study medication and the other was judged as unrelated.

Three adverse events were judged as significant by the principal investigator, and all were considered possibly related to the study medication. One patient in the 4mg group developed a breast lump which was excised and found to be benign. One patient in the 2mg group had an episode of respiratory distress and the study medication was discontinued. One patient in the 1mg group developed hypertension after 6 weeks and the treatment was discontinued and she was subsequently diagnosed with hyperthyroidism.

There were no relevant changes in any haematological or biochemical laboratory measurements during the course of the study.

Study A01177

A total of 104 patients were included in this uncontrolled study to receive DNG 1mg twice daily for 24 weeks and thus comprised the FAS for safety evaluation. Patients were assessed at baseline, and subsequently at 1, 3 and 6 Months during and at 1 and 3 Months after treatment and were questioned about side effects of DNG while avoiding leading questions.

Overall, a total of 174 AEs were reported in 52 (50.0%) of the patients. There was no assessment of causality of AE and so all of the AEs reported were considered to be possibly related to the study medication. The most frequent AEs were decreased libido (21.2%), fatigue (9.6%), increased appetite (8.7%), nausea (6.7%), hot flushes (5.8%) and acne (5.8%). Other AEs recorded for <5% of patients included headache, breast pain, and irritability.

There were no deaths or serious AEs reported. None of the AEs led to premature discontinuation of the study.

The majority of patients (88.1%, 89 of 101 – excluding 2 patients post hysterectomy and one had no data recorded) experienced at least one episode of breakthrough bleeding, and 58.4% experienced more than three events during the treatment period; 12 patients were amenorrhoeic throughout the study. Bleeding seemed to decrease throughout the study and during Months 4-6, amenorrhoea was reported in 33.7% of women.

There were no significant changes in vital signs during the study. Weight gain >2kg was reported in 37.5% and weight loss >2kg was reported in 23%. Regarding laboratory data, the only reported significant changes were for high density lipoprotein (HDL) cholesterol with a maximal deviation from baseline of -5.8% and low density lipoprotein (LDL) cholesterol with a maximal deviation from baseline of +5.0%.

Study A01176

A total of 167 patients were enrolled in this open label study comparing the effects of DNG 1mg twice daily (119 patients) and NETA 5mg twice daily (48 patients) for a treatment duration of 24 weeks, thus comprising the FAS for safety. The patients were assessed at baseline, and Months 1, 3 and 6 during the study and Months 1 and 3 after EOT. They were questioned about the side effects of either DNG or NETA, with avoidance of leading questions, and compliance and bleeding pattern data were obtained from patient diaries. Potential causality was not assessed during the evaluation and therefore all AEs were considered potentially treatment related.

There were a total of 521 AEs reported in 71 (59.7%) of patients in the DNG group. The most frequent of these were increased appetite (37.0%), loss of libido (35.3%), hot flushes (18.5%), headache (17.6%), irritability (16.0%), headache (16.0%), acne (15.1%), and fatigue (14.3%).

In the NETA group, there were 174 AEs reported in 31 (64.6%) patients. The most frequent were loss of libido (35.4%), increased appetite (33.3%), hot flushes (14.6%), decreased efficiency (14.6%), headache (12.5%), irritability (10.5%), and acne (10.4%). In both groups, the side effects are reported as mild and transitory, although comment is made that under both treatments a significant number of women who experienced reduction in libido did so throughout the trial period.

There were no reported deaths, serious AEs or premature discontinuations due to AEs.

In the DNG group, 76.3% of women experienced at least one event of breakthrough bleeding during the study. This was mostly of spotting intensity, and decreased with treatment duration resulting in 37.3% with amenorrhoea during months 4-6 of treatment. For the NETA group, 60.4% of women experienced at least one event of breakthrough bleeding. Again, this was predominantly of spotting

intensity and reduced throughout treatment so that during months 4-6, 58.3% of patients had amenorrhoea.

There were no clinically relevant changes in vital signs during treatment in either group. Regarding weight, 28.6% of patients on DNG had gained ≥2kg whereas 5.9% lost ≥2kg. In the NETA group, 50.0% had gained ≥2kg and 4.2% lost ≥2kg.

Laboratory parameters analysed included urinalysis, haematology, biochemistry, liver enzymes and lipid profile. In the DNG group, there were no significant changes outside of the normal range. Regarding the lipid profile, the maximum deviation from baseline was -5.2% for HDL cholesterol and +3.6% for LDL cholesterol. In the NETA group, the ALT exceeded normal range after 3 months of treatment. Regarding the lipid profile, the maximum deviation of HDL from baseline was -22.3% after 3 months, and for LDL was +16.1%.

Safety: Trials for other indications and dosage

Study A04431

This was a high dose pilot study to investigate the effect of DNG 2 x 10mg on endometriosis in women with laparoscopically proven disease. A total of 23 patients were enrolled, and were planned to take the medication for a period of 24 weeks. The FAS consisted of 21 patients because 2 of the women did not take any of the study medication.

A total of 102 AEs were reported in the study affecting 100% of patients. Of these, 36 were recorded as spontaneous/ unexpected and 66 as expected. The most frequent of the spontaneously reported AEs were common cold/ sore throat (6 occurrences in 6 patients), gastritis/ gastroenteritis (3 mentions in 3 patients) and hot flushes (3 mentions in 3 patients). The most frequent of the expected AEs were breast pain (14 times in 12 patients), headache (10 times in 9 patients), depressive mood (8 mentions in 7 patients), nausea/ vomiting (6 mentions in 4 patients) and alopecia (6 times in 4 patients). From the total number of AEs, 82 (80.4%) were considered to have a possible or probable relationship to the study medication.

There were no deaths, serious AEs or events leading to discontinuation of the study medication. One patient temporarily interrupted the study medication due to gastritis. Three of the AEs were judged as clinically severe, one case of increased breast pain, one case of migraine and one case of tonsillitis.

Findings for standard laboratory markers were unremarkable. There were minor effects on the lipid profile. Liver function tests were stable apart from a mild increase in alkaline phosphatase. There were effects on coagulation parameters which were balanced changes in anti-thrombotic and fibrinolytic factors.

Study B567

This was a multicentre, randomised, open label, parallel group study comparing the efficacy of DNG (1mg twice daily) versus Decapeptyl in the consolidation of surgery for endometriosis. Decapeptyl is a GnRH analogue (triptorelin) and is administered as a 3.75mg intramuscular injection monthly. The initial study included 144 women between 18 and 40 years of age with known endometriosis, 140 of whom received at least one dose of study medication and comprised the FAS for safety evaluation (73 patients treated with DNG, and 67 with Decapeptyl). Adverse effects in the study were recorded by the investigators after direct questioning, and examining the patient diaries for spontaneously reported AEs.

A total of 459 AEs occurred in 68 patients in the DNG group (93.2%) compared to 320 AEs in 61 patients in the Decapeptyl group (91.0%). The most frequent AEs in the DNG group were metrorrhagia (71.2%), headache (30.1%), pelvic pain (21.9%), abdominal pain (15.1%),

nasopharyngitis (13.7%), nausea (13.7%), and hot flushes (12.3%). In the Decapeptyl group, the most frequent AEs were hot flushes (58.2%), metrorrhagia (34.3%), headache (34.3%), pelvic pain (20.9%), abdominal pain (14.9%), migraine (11.9%), nausea (10.4%), and vulvovaginal dryness (10.4%).

There were 27 AEs reported as severe in the DNG group in 20 patients, compared to 41 severe AEs in 27 patients in the Decapeptyl group. The following severe AEs were reported for more than one patient in the DNG group: metrorrhagia (6.8%) and pelvic pain (2.7%). Similarly, in the Decapeptyl group, hot flushes (17.9%), vulvovaginal dryness (4.5%), insomnia (4.5%), migraine (4.5%), headache (4.5%), cardiac flutter (3.0%), and lower abdominal pain (3.0%) were reported or more than one patient.

There were no deaths during the study. There were 2 patients who developed serious AEs during treatment. One patient in the DNG group was hospitalised for ureteric stenosis, and one patient in the Decapeptyl group was hospitalised for abdominal pain 4 months after her last injection of the study medication. Neither of these events was considered causally related to the study medication. Four patients in the DNG group prematurely discontinued the medication due to AEs. One patient who had raised blood glucose on enrolment in the study was diagnosed with diabetes, and her DNG was discontinued. One patient developed upper abdominal pain. One patient with recurrent migraines developed a migraine within the first week of treatment, and one patient developed metrorrhagia. In all of these cases the relationship to study medication was rated by investigators as "not excluded". In the Decapeptyl group, one patient discontinued the medication due to abdominal pain, hot flushes and headache.

Neither treatment significantly affected vital signs throughout the study. Regarding laboratory data, in the DNG group, two patients had increased blood glucose and two had increased cholesterol, and one patient each had raised triglyceride or aspartate aminotransferase (AST). In the Decapeptyl group there was a clinically relevant increase in cholesterol levels in 11 patients, 4 patients had a raised blood glucose, 2 with raised AST, and one each with raised triglycerides, ALT and alkaline phosphatase (AP).

Overall the safety profile was acceptable for both drugs, with >80% of patients in both groups being generally satisfied with thee treatment. Spotting was more frequent in the DNG group whereas hot flushes were more frequent in the Decapeptyl group.

Study A05436

This was a multicenter, open, randomised, 2-arm, phase 2 clinical study to compare the efficacy of Visanne (DNG 2mg once daily) with LA in preparing the endometrium for ablation over a period of 8 weeks. A total of 75 women aged between 18 and 55 years were randomised and received either Visanne (37 patients) or LA (38 patients). Safety was assessed by reporting of AEs, laboratory parameters, and physical examination.

There was a total of 193 AEs in 55 patients reported during the study. In the DNG group, there were 63 AEs in 21 patients (56.8%), and in the LA group there were 130 AEs in 34 patients (89.5%). The most frequent AEs in the DNG group were breast pain (13.5% of patients), headache (13.5%), hot flushes (13.5%), sleep disorders (13.5%), acne (8.1%), and vaginal discomfort (8.1%). In the LA group the most frequently reported AEs were hot flushes (57.9% of patients), sleep disorder (36.8%), headache (23.7%), vaginal discomfort (18.4%), abdominal pain (18.4%), and tachycardia (13.2%). With regards to suspected association with the study medication, ADRs (that is, AEs with possible, probable or confirmed association) were less frequent ion the DNG group (54.0%) compared to the LA group (82.3%).

During this study, there were no deaths, serious AEs, or AEs that led to premature discontinuation of study medication.

There were no significant abnormalities in vital signs or gynaecological examination in either group. Neither of the two treatments induced significant changes in the mean value of any laboratory parameter. LA appeared to cause an increase of abnormalities of liver enzymes. In both treatment groups, there was an increase in frequency of LDL cholesterol levels above normal range at EOT (from 5.4% to 22.2% with DNG; from 5.3% to 18.5% for LA).

Summary of Safety

In the above nine trials, a total of 727 women were exposed to DNG 2mg per day or more for duration of up to 72 weeks.

A pooled analysis of the four studies (A32473, AU19, A39700 and A02266) which specifically looked at Visanne (that is, DNG 2mg once daily) was also provided by the sponsor, which incorporated 332 women who were treated with Visanne, in comparison to placebo, LA and DNG 4mg daily.

Across these trials, the most common adverse effects with at least a possible causal relationship to Visanne (that is, ADRs) were headache (9.0% of patients), acne (5.1%), nausea (4.2%), increased weight (3.6%), breast discomfort (3.3%), depressed mood (3.0%) and flatulence (3.0%).

There were minimal androgenic effects, as demonstrated by no unfavourable effects on lipid metabolism, and only mild oestrogen deficiency effects (some hot flushes but less than with the GnRH analogues). Oestrogen levels were mildly suppressed in the two pivotal clinical trials (A32743 and AU19). Data regarding effects on BMD are scant, and appeared contradictory depending on whether the FAS patients or only patients with matched pre and post treatment DEXA scan BMD values were analysed.

Furthermore, doses of 4mg DNG and 20mg DNG were tolerated in two other studies for up to 24 weeks with no significant adverse effects.

With regard to bleeding patterns, in both pivotal clinical trials (AU19 and A32473) and in the extension study (A39700) (where uterine bleeding was a primary efficacy outcome), a large number of patients experienced abnormal bleeding patterns compared to normal menstrual cycle. Across all the studies, over time, the frequency and intensity of bleeding reduced with time. In the extension study A39700, incidence of irregular and prolonged bleeding decreased consistently, with more patients experiencing amenorrhoea at end of trial. These bleeding abnormalities are similar to those reported for other progestin only preparations in endometriosis[xxv]. Despite the observed degree of abnormal bleeding, dropout rate due to this was low. In addition, haematological parameters were very stable across all studies, suggesting that the abnormal uterine bleeding was not clinically significant enough to amount to a safety concern.

Safety Conclusions

- *The safety of Visanne has been demonstrated in 4 clinical studies involving 322 women and supporting evidence of the safety of dienogest 2mg or more daily is supplied from a further 5 studies.*
- *There were no androgenic effects noted (no unfavourable effects on lipid metabolism) which is advantageous compared to drugs such as danazol.*
- *Oestrogen levels were only moderately suppressed, and much less than that which occurred with GnRH analogues (study AU19). Oestrogen deficiency related adverse effects were less common than with GnRH analogues.*
- *There was lesser reduction in BMD in a small sample compared to GnRH analogues.*
- *The most common ADRs associated with DNG treatment were headache, breast discomfort, depressed mood and acne.*

- *Visanne also leads to menstrual irregularity and spotting, although there were no cases of significantly abnormal haematological parameters as a result of abnormal uterine bleeding.*

Post-marketing Experience

As Visanne has not been marketed elsewhere, there are no Periodic Safety Update Reports (PSURs) regarding its use. PSURs were submitted for the combination products Climodien (DNG 2mg + EV 2mg) used for hormone replacement therapy in post menopausal women, and Valette (DNG 2mg + EE 30µg) used as a combined oral contraceptive. However, due to both of these products being combination medications, it is difficult to extrapolate any data to experiences with DNG alone.

As an addition to the initial submission, in August 2009, a safety update regarding potential serious uterine bleeding was forwarded to the evaluator. This was based on 17 cases of serious uterine bleeding in association with a product called "Dinagest" which had been reported to Bayer Pharma Pharmacovigilance up until May 2009. Dinagest tablets contain 1mg DNG and are marketed in Japan by Mochida as a treatment for endometriosis.

Ten out of 17 women were hospitalised due to severe metrorrhagia. The age of patients ranged between 33 and 49, with onset of serious uterine bleeding occurring between commencing therapy and three months. In 13 out of 17 cases, significant anaemia was reported with haemoglobin (Hb) values between 4.7g/dl and 8g/dl (normal >12g/dl), with the most serious case report of a 46 year old woman with haemorrhagic shock (dizziness, blood pressure 70/38 mmHg) requiring endometrial cautery and red cell transfusion. Ten of the 17 women had known history of uterine bleeding disorders and a total of 16 had either adenomyosis or uterine leiomyomata as concurrent medical conditions which were considered by the sponsor as most likely responsible for the bleeding. The pre-existing bleeding disorder may have been aggravated by use of Dinagest.

Despite no reports of serious bleeding disorders occurring in the clinical trials with Visanne, the sponsor has updated the PI by adding a precaution statement regarding changes in bleeding pattern occurring during treatment.

Clinical Summary and Conclusions

Recommendation

On balance of its demonstrated clinical efficacy and favourable safety profile when compared to other existing treatment options for endometriosis, the evaluator recommends approval to register Visanne for the treatment of endometriosis. However, as discussed in the Efficacy Section, further data regarding rescue medication for endometriosis-related pain needs to be provided to clarify long-term efficacy.

V. Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission.

VI. Overall Conclusion and Risk/Benefit Assessment

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

Quality

All chemistry and quality control issues have been resolved. The stability data support the proposed shelf life of 5 years when stored below 25 ^{0} C in PVC/Al blister packs. Two bioavailability studies were provided: the absolute bioavailability was 91%; food had no effect on bioavailability.

The evaluator recommended approval.

Nonclinical

The evaluator indicated that adequate nonclinical data were submitted to support this application.

Two studies examined the effects of dienogest in an experimental model of endometriosis in rats. Both studies showed results consistent with efficacy in the treatment of endometriosis.

The evaluator noted that previous applications have included safety studies conducted with dienogest alone and is of the opinion that the existing non-clinical data are adequate for the registration of Visanne.

The effect on bone mineral density has not been discussed.

Overall, the evaluator recommended approval from a nonclinical point of view.

Clinical

Pharmacodynamic studies: The evaluator reviewed six pharmacodynamic studies; five of these studies were conducted on healthy female volunteers.

The first study, **B468** examined the antigonadotrophic activity of dienogest (part 1 of the study) and also the endometrial transformational dose of dienogest (part II of the study). Part I involved 21 women (who were eumenorrhoeic or oophorectomised). They received 0.2mg or 0.4mg of dienogest or levonorgestrel for 21 days and their blood levels for LH, oestradiol, progesterone and FSH were measured. Suppression of these levels was seen both with dienogest and levonorgestrel in eumenorrhoeic women. There were no effects seen in the oophorectomised women. In the second part of the study, daily dienogest doses of 0.35mg, 0.45mg and 0.55 mg were given. There was secretory transformation observed after the 0.45mg dose.

Dose response was also assessed in study **A03128**, where 40 women (postmenopausal or oophorectomised) were administered 50 µg ethinyloestradiol for 14 days followed by 50 µg ethinyloestradiol + 0.25, 0.35, 0.45 or 0.55 mg dienogest. Endometrial biopsies were taken on Day 15 and Day 29. There was a suggestion that all doses produced secretory transformation; the minimum transformation dose could not be identified.

Study **B470** was performed to determine the ovulation inhibition dose of dienogest in healthy women (n=30) between the ages of 20- 29 years. They received 0.5, 1.0, 1.5mg or 2 mg dienogest for 21 days commencing Day 5 of the menstrual cycle. Ovulation inhibition (progesterone levels < 3.5 nmol/L) was seen at doses ≥ 1.5mg dienogest. The evidence at 1.0mg was less convincing.

Another study **A02263** showed that 2 mg dienogest did not completely inhibit follicular maturation when administered for 21 days.

The evaluator also discussed a study on 55 women who were investigated for the potential of 3 mg dienogest and 2 mg oestradiol valerate as a fixed dose combination to delay cardiac repolarisation. There was no effect observed in relation to cardiac repolarisation using several doses. However, this was a study on a small number of healthy women.

Patient pharmacodynamics: Study **A05436** compared the efficacy of dienogest to that of leuprorelin acetate in preparing the endometrium for endometrial ablation in patients with refractory uterine bleeding. A total of 75 women were enrolled, 37 in the dienogest group and 38 in the leuprorelin acetate group. Dienogest, 2 mg was administered daily for 56 days and 3.75 mg leuprorelin acetate was administered as IM injections every 28 days (two injections in total).

Several efficacy endpoints were used. The evaluator noted that though there was adequate suppression with dienogest, leuprorelin acetate fared better in comparison.

Overall, these studies showed that dienogest has progestogenic actions as seen by its ability to induce endometrial transformation. The minimum effective dose was not identified. There was conflicting results in relation to its antigonadotrophic effects (see Study **A02263** and Study **B468**).

A dose of ≥ 1.5 mg was required for ovulation suppression. 2mg dienogest appeared adequate for endometrial preparation prior to ablation surgery; it was not as effective as leuprorelin acetate. There appeared to be no observed effect on cardiac repolarisation with doses in the therapeutic range or supratherapeutic range. A 2mg dose inhibits ovulation but ovarian hormone production is not entirely suppressed.

Pharmacokinetics

Three bioavailability studies were discussed. These have been conducted in young healthy males. The evaluator indicated that the study in males "is justified in the submission because the studies investigate formulation effects by intra-individual comparison, so selected study population should not affect validity". The absolute bioavailability of the tablet was 90.6% (90% CI: 86.6-94.7). The relative bioavailability of the proposed tablet form compared to a microcrystalline formulation was 100%. Food had little effect on bioavailability.

Study **B306** was a randomised 4 way crossover study on 14 healthy females aged 18- 40 years. Four treatments were administered (1, 2, 3 or 8mg) as a single dose in the first 7 days of the menstrual cycle. C_{max} and AUC showed dose linear kinetics.

Study **B276** investigated the single and repeat dose pharmacokinetics (over 14 days) in 16 healthy female volunteers (18-40 years). This study showed that the mean trough levels reached a plateau in 4 days. There was accumulation seen with repeat doses (2mg/day for 14 days) with the accumulation ratio being 1.2 and the terminal half live being 8-10 hours.

A study (**B478**) which used ^{3}H-labelled dienogest following 0.1 mg/kg in 6 healthy young females showed that within 24 hours of administration 60% of the total radioactivity was attributable to unchanged dienogest; there was no other peak besides unchanged dienogest. Only 1% was excreted unchanged in the urine.

Four drug interaction studies were conducted. Of importance to this submission are three of these studies. Study **AR34** showed bioequivalence of dienogest when administered alone compared with the fixed combination with oestradiol valerate (2mg oestradiol valerate and 3 mg dienogest). Dienogest is metabolised by CYP 3A4. **Study** A**24058** examined the effect of an inducer and Study **A30020** examined the effects of two inhibitors. **Study** A**24058** was conducted on 16 post menopausal women, where the subjects were administered a fixed dose combination of 2 mg oestradiol valerate and 3 mg dienogest for 17 days. 600 mg of rifampicin was administered daily on Days 12 to 16. There was a significant reduction in dienogest AUC and C_{max}-The geometric mean ratio of AUC (Day 17 versus Day 11) was 17% (90%-CI: 15.6 – 18.7). The geometric mean ratio of C_{max} (Day 17 versus Day 11) was 48% (90%-CI: 44.8 – 51.6). Study **A30020** was also conducted on healthy postmenopausal women (n=24) where the effect of erythromycin and ketoconazole on the pharmacokinetics of dienogest was examined. There was a significant increase in C_{max} and AUC.

Efficacy:

Phase II

Study A02266 is a phase 2 dose finding study comparing 1, 2 and 4 mg dienogest administered daily for 24 weeks. Women between menarche and menopause with laparascopically confirmed endometriosis are included. 68 patients were enrolled. 4 in the 1 mg group; 29 in the 2 mg group and 35 in the 4 mg group. (1 mg was stopped due to lack of effect). This study examined the reduction of endometriotic lesions. There was no significant difference between the two groups in the small number of women recruited.

Phase III

The evaluator reviewed two pivotal phase III studies that assessed the reduction of symptoms of endometriosis. **Study A32473** was a placebo controlled study and **Study AU19** used leuprorelin

acetate as a comparator. **Study A39700** is a one year extension study of the former study that assessed sustained improvement.

There were also two studies **A01177** and **A01176** that were pre-GCP studies that will be discussed briefly. These are considered supporting data only.

Study **A32473** was a multicentre double blind randomised study comparing 2 mg dienogest/day versus placebo in women with endometriosis; the study duration was 12 weeks.

The inclusion criteria were women of child bearing age (18-45) who complained of pain associated with histologically proven endometriosis (stages I- IV according to revised American Society for Reproductive Medicine classification of endometriosis score: r-ASRM score), as determined by diagnostic laparoscopy within 12 months prior to onset of treatment but no later than 6 weeks prior to screening. The baseline pain score was to be at least 30 mm on visual analogue score (VAS) and be willing to use barrier contraception. Exclusion criteria mentioned the previous use of other hormonal agents. Those with co-morbidities were also excluded.

The primary efficacy endpoint was the reduction of EAPP-this was assessed by the change of VAS and the change of intake of rescue medication between baseline and end of treatment. The secondary efficacy outcomes included intake of rescue medication, B&B severity profile for symptoms and quality of life assessment.

It is stated that to account for multiple endpoints, the 3 step hierarchical testing procedure of Rohmel and others was employed, which consists of 1) demonstration of non-inferiority, 2) Laeuter's one sided standard sum test for overall demonstration of superiority of DNG over placebo and 3) test of superiority of DNG versus placebo for each of the two primary variables.

The evaluator discussed the results according to the three step hierarchical procedure. The results of the initial two steps allowed for the third step where there was statistical superiority in terms of VAS, but not in terms of the reduction of rescue medication.

The evaluator observed that despite a noticeable placebo effect, this reduction of EAPP is clinically as well as statistically significant, with a difference between the mean reductions of VAS of 12.27mm. The evaluator noted that the secondary efficacy analyses were in line with the primary endpoints; however, no statistical analyses were performed.

Though study **AU19** is claimed to be pivotal, this uses a comparator that is not registered in Australia; in that context, it should be considered a supportive study. This is an open label multicenter study of 2mg dienogest versus IM administration of 3.75 mg leuprorelin acetate every 4 weeks in the treatment of symptomatic endometriosis, over 24 weeks.

The primary efficacy endpoint was the change in pelvic pain from baseline to end of treatment as assessed by VAS. The secondary efficacy endpoints were similar to those of the previous study.

Women of child bearing age between 18 to 45 years with pain associated with histologically proven endometriosis were recruited. Other selection criteria were similar to the previous study.

Non-inferiority between dienogest and leuprorelin acetate was defined as a difference between VAS scores at end of trial of $\leq$15mm between the leuprorelin acetate group and dienogest group.

The following results were observed:

Table 30. Study AU19

Mean VAS results (in mm) at each visit (PP)

Time	DNG group			LA group		
	n	mean	SD	n	mean	SD
screening	90	60.2	24.2	96	57.9	21.0
week 4	90	35.7	23.7	96	32.6	27.0
week 8	90	24.2	22.5	96	21.7	23.0
week 12	90	19.7	23.2	96	18.7	23.0
week 16	90	16.2	20.2	96	14.6	19.5
week 20	90	12.5	18.0	96	12.8	19.0
week 24	90	12.7	20.3	96	11.9	16.9

Table 31. Study AU19

Summary of the analyses of the primary target variable (PP and FAS)

Analysis set	DNG group (mean)	LA group (mean)	difference of means (DNG – LA)	two-sided 95% confidence interval for difference of means	one-sided p-value
PP	-47.5111	-46.0104	-1.5007	[-9.2552, 6.2539]	<0.0001
FAS	-40.1760	-41.7565	1.5806	[-6.4145, 9.5756]	0.0004

The evaluator mentions that non-inferiority was seen in relation to the primary endpoint; however, the magnitude of change was greatest in the first 4 weeks.

The secondary efficacy endpoints (pelvic pain over time), use of rescue medications, B&B score and Quality of Life questionnaire (QoL) showed non-inferiority between treatment groups.

Study A39700: This is a 52 week extension of study **A32473**. Those who completed A32473 were eligible to enrol: this was a total of 168 patients. The primary endpoint was uterine bleeding pattern; this was assessed every 90 days. The following results were observed:

The number (mean ±SD) of bleeding/ spotting days:

<u>the first 90-day period</u> <u>the fourth 90 day period</u>

20.2 (±15.2) 9.7 (±9.0)

<u>the number of bleeding/spotting episodes</u>

3.0 (±1.8) 2.0 (±1.6).

The previous placebo group displayed a higher number of bleeding/ spotting days (24.5±16.4) and bleeding/spotting episodes (3.2±1.8) compared to previous dienogest group (16.3±13.0 bleeding/spotting days and 2.8 ±1.8 bleeding/spotting episodes). Both groups had a reduction in numbers of bleeding/spotting days at end of the fourth 90-day period to 10.1±8.7 in the placebo group and 9.4±9.3 in the dienogest group. Reduction in number of bleeding/spotting episodes was also observed after the fourth 90-day period to 2.1 ±1.6 in the placebo group and 1.9±1.5 in the previous dienogest group.

These results indicate that the effect is sustained. However, the evaluator noted that approximately 25% of patients used some concomitant analgesia during the study.

Two pre-GCP studies (A01177 and A01176) used a different dosing regimen, 1 mg twice a day (b.d.) and are of limited relevance.

Safety

Over 727 women were exposed to 2 mg dienogest. The evaluator noted a pooled analysis of four studies (A 32743, AU19, A39700 and A02266) which included 332 females treated with 2 mg dienogest; this was compared to placebo, leuprorelin acetate and dienogest 4mg.

The evaluator indicated that the most common adverse events where dienogest could be implicated were headache (9%), acne (5.1%), nausea (4.2%), increased weight (3.6%), breast discomfort (3.3%) , depressed mood (3.0%) and flatulence (3.0%).

The evaluator also noted that in the pivotal and extension studies, there were a large number of patients who experienced abnormal bleeding patterns compared to normal menstrual cycle.

There were minimal androgenic effects and only mild oestrogenic deficiency effects.

BMD of the lumbar spine was measured in Study **AU19** . This study lacked a positive control-that is, danazol or placebo. BMD was measured in a subgroup of patients from three study centres at baseline and at the end of treatment (24 weeks). Those with a baseline BMD > 2.5 below the standard deviation were excluded. A total of 64 patients (26 in dienogest and 31 in leuprorelin acetate groups) were included in the full analysis set (FAS). There was an overall change in the mean of -0.0254g/cm^2 for the dienogest group and -0.0569g/cm^2 in the leuprorelin acetate group. However the report states that in those with both the baseline and end of treatment values, the following was observed: +0.0022g/cm^2 in the dienogest group (n=21) and of -0.0415g/cm^2 in the leuprorelin group (n=29). Clearly the numbers are inadequate to be conclusive. More data (that is more numbers and longer duration) are required to assess the effect of dienogest on BMD.

Recommendation

Overall, there is evidence presented that symptoms of endometriosis are reduced significantly compared with placebo. Non-inferiority relating to these symptoms was also seen in comparison to leuprorelin acetate. There was maintenance of efficacy seen in an extension study of 12 months. In relation to safety the evaluator noted that the common effects were headache, breast discomfort and depression. There were also menstrual irregularities observed. The evaluator also noted that the symptoms relating to hypo-oestrogenic state (hot flushes, reduced BMD) would be less than with GnRH analogues; androgenic adverse effects should be less than those caused by danazol. However, no studies have been submitted where a direct comparison has been made with registered products in Australia.

Overall, the evaluator recommends approval.

Risk-Benefit Analysis

1. Two clinical studies show evidence of efficacy of dienogest in endometriosis; the first study (**A32473**) is a placebo controlled study that showed superior efficacy in relation to symptoms of endometriosis. The second study (**AU19**), unfortunately is of limited relevance in the Australian setting because the comparator used in this study is not registered for endometriosis. This study also supports efficacy in relation to the symptoms of endometriosis. It is noted that improvement in fertility has not been a measured endpoint in these studies.
2. A deficiency in this submission is the lack of good quality data of the effect of dienogest on BMD. The data at 24 weeks is inconclusive because of the small number of subjects involved in the analysis. More data are needed to ascertain the effect of dienogest on BMD. This lack of data should be addressed in the PI.
3. The lack of BMD data impacts on the duration of treatment that is considered safe. Both pivotal studies only provide short term efficacy results; the long term extension does not have data on BMD.
4. There are no data on switching from other treatments. The two efficacy studies did specify that there be an interval of three months without treatment for endometriosis, to be eligible to

participate in the study. Thus, the effect of concomitant therapy or switching from one agent to the other, have not been investigated. These should be addressed in the PI.

5. At this stage, it is recommended that the duration of treatment be restricted to 6 months till further data are provided on the effect or (lack of it) on BMD.

The Delegate proposed that dienogest 2 mg (Visanne) be recommended for the short term treatment of endometriosis.

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended approval of the submission from Bayer Australia Ltd to register the new chemical entity of Dienogest (VISANNE) tablet 2 mg for the indication:

Treatment of endometriosis

In making this recommendation the ACPM considered the lack of evidence with respect to the long term safety of the treatment in terms of Bone Mineral Density (BMD), noting that both pivotal studies only provide short term efficacy results and that the long term extension does not have data on BMD. The ACPM advised that it is appropriate to not limit the duration of therapy to 6 months provided there is a provision for regular checks on BMD. Further, the ACPM noted that as the effect of switching from one agent to the other has not been investigated, considerations of this matter should be addressed in the product information.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Visanne, as dienogest, 2 mg tablets in blister pack, indicated for:

The treatment of endometriosis.

Attachment 1. Product Information

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

Appendix 1 References

(A)

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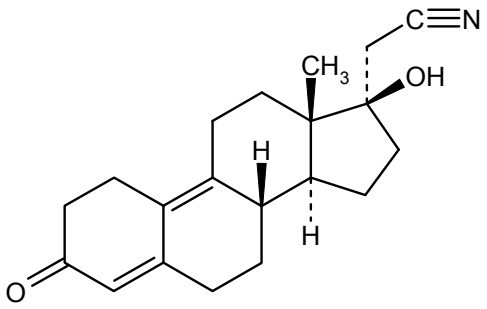
PRODUCT INFORMATION
VISANNE®

DESCRIPTION

Each Visanne tablet contains 2 mg of dienogest. The tablets are white to off-white, round, flat- faced, bevelled edge with an embossed “B” on one side and have a diameter of 7 mm.

The chemical structure of dienogest is as follows;



INN	Dienogest
IUPAC / WHO	17α-Hydroxy-3-oxo-19-norpregna-4,9-diene-21-nitrile (IUPAC)
CAS No	65928-58-7
Molecular formula	C_{20} H_{25} N O_2
Molecular weight	311.43
Appearance	White to off-white crystalline powder

In addition Visanne contains the following inactive ingredients: lactose, potato starch, microcrystalline cellulose, povidone, talc-purified, crospovidone, magnesium stearate, water-purified.

PHARMACOLOGY

Pharmacotherapeutic group: Progestogens

ATC code: G03D
Dienogest is a nortestosterone derivative with 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 oestradiol and thereby suppressing the trophic effects of oestradiol on both the eutopic and ectopic endometrium. When given continuously, dienogest leads to a hypoestrogenic, hypergestagenic endocrine environment causing initial decidualisation of endometrial tissue followed by atrophy of endometriotic lesions. Additional properties, like immunologic and antiangiogenic effects, seem to contribute to the inhibitory action of dienogest on cell proliferation.

Pharmacokinetic properties

- Absorption

Orally administered dienogest is rapidly and almost completely absorbed. Peak serum concentrations of approximately 47 nanograms per mL are reached at about 1.5 hours after single ingestion. Bioavailability is about 91%. The pharmacokinetics of dienogest are dose-proportional within the dose range of 1 – 8 mg.

- Distribution

Dienogest is bound to serum albumin and does not bind to sex hormone binding globulin (SHBG) or corticoid binding globulin (CBG). 10% of the total serum drug concentrations are present as free steroid, 90% are non-specifically bound to albumin.

The apparent volume of distribution (V_d/F) of dienogest is 40 L.

- Metabolism

Dienogest is completely metabolised by the known pathways of steroid metabolism, with the formation of endocrinologically mostly inactive metabolites. Based on *in vitro* and *in vivo* studies, CYP3A4 is the major enzyme involved in the metabolism of dienogest. The metabolites are excreted very quickly so that in plasma unchanged dienogest is the dominating fraction.

The metabolic clearance rate from serum Cl/F is 64 mL/min.

- Elimination

Dienogest serum levels decrease in two phases. The terminal disposition phase is characterised by a half-life of approximately 9-10 hours. Dienogest is excreted in the form of metabolites which are excreted at a urinary to faecal ratio of about 3:1 after oral administration of 0.1 mg/kg. The half-life of urinary

metabolites excretion is 14 hours. Following oral administration approximately 86% of the dose administered is eliminated within 6 days, the bulk of this amount is excreted within the first 24 h, mostly with the urine.

- Steady-state conditions

Pharmacokinetics of dienogest are not influenced by SHBG levels. Following daily ingestion, drug serum levels increase about 1.24 fold reaching steady-state conditions after 4 days of treatment. The pharmacokinetics of dienogest after repeated administration of Visanne can be predicted from single dose pharmacokinetics.

CLINICAL TRIALS

- Efficacy

Superiority of Visanne over placebo with regard to reduction of endometriosis-associated pelvic pain (EAPP) and clinically meaningful reduction of pain compared to baseline were demonstrated in a 3-month study including 102 patients on Visanne. EAPP was measured on a Visual Analog Scale (VAS) (0 – 100 mm). After 3 months of treatment with Visanne, a statistically significant difference compared to placebo (Δ = 12.3 mm; 95% CI: 6.4 – 18.1; $p < 0.0001$) and a clinically meaningful reduction of pain compared to baseline (mean reduction = 27.4 mm ± 22.9) were demonstrated.

After 3 months of treatment, reduction of EAPP by 50% or more without relevant increase of concomitant pain medication was achieved in 37.3% of patients on Visanne (placebo: 19.8%); a reduction of EAPP by 75% or more without relevant increase of concomitant pain medication was achieved in 18.6% of patients on Visanne (placebo: 7.3%).

The open-label extension to this placebo-controlled study showed a continued improvement of endometriosis-associated pelvic pain for a treatment duration of up to 15 months (mean reduction at end of treatment = 43.2 ± 21.7 mm).

In addition, efficacy on endometriosis-associated pelvic pain was shown in a 6-months comparative trial of Visanne versus the GnRH analogue leuprorelin acetate (LA) including 120 patients on Visanne. EAPP was measured on a VAS (0 – 100 mm). A clinically meaningful reduction of pain compared to baseline and statistical non-inferiority versus LA were demonstrated (Visanne 47.5 ± 28.8 mm, LA 46.0 ± 24.8 mm). Non-inferiority versus LA based on a pre-defined non-inferiority margin of 15 mm was demonstrated ($p < 0.0001$).

Three studies including a total of 252 patients who received a daily dose of 2 mg dienogest demonstrated a substantial reduction of endometriotic lesions after 6 months of treatment.

In a small study (n=8 per dose group), a daily dose of 1 mg dienogest has been shown to induce an anovulatory state after 1 month of treatment. Visanne has not been tested for contraceptive efficacy in larger studies.

- Safety

Endogenous oestrogen levels are only moderately suppressed during treatment with Visanne.

Bone mineral density (BMD) was assessed in a small group of patients (n=21) before and after 6 months of treatment and there was no reduction in the mean BMD. If clinically warranted BMD may be monitored and the results used in the risk-benefit assessment of use of Visanne

No significant impact on standard laboratory parameters, including haematology, blood chemistry, liver enzymes, lipids, and HbA1C was observed during treatment with Visanne for up to 15 months (n=168).

INDICATIONS

Treatment of endometriosis.

CONTRAINDICATIONS

Visanne should not be used in the presence of any of the conditions listed below, which are partially derived from information on other progestogen-only preparations. Should any of the conditions appear during the use of Visanne, the use of the preparation must be discontinued immediately.

- Known or suspected pregnancy
- Lactation
- Active venous thromboembolic disorder
- Arterial and cardiovascular disease, present or in history (e.g. myocardial infarction, cerebrovascular accident, ischaemic heart disease)
- Diabetes mellitus with vascular involvement
- Present or history of severe hepatic disease as long as liver function values have not returned to normal
- Present or history of liver tumours (benign or malignant)
- Known or suspected sex hormone-dependent malignancies
- Undiagnosed vaginal bleeding
- Hypersensitivity to the active substance or to any of the excipients.

PRECAUTIONS

General

As Visanne is a progestogen-only preparation it can be assumed that special warnings and special precautions for use of other progestogen-only

preparations are also valid for the use of Visanne although not all of the warnings and precautions are based on respective findings in the clinical studies with Visanne.

If any of the conditions/risk factors mentioned below is present or deteriorates, an individual risk-benefit analysis should be done before Visanne is started or continued.

Circulatory disorders
From epidemiological studies there is little evidence of an association between progestogen-only preparations and an increased risk of myocardial infarction or cerebral thromboembolism. The risk of cardiovascular and cerebral events is related to increasing age, hypertension, and smoking. In women with hypertension the risk of stroke may be slightly enhanced by progestogen-only preparations.

Some studies indicate that there may be a slightly, but not statistically significant increased risk of venous thromboembolism (deep venous thrombosis, pulmonary embolism) associated with the use of progestogen-only preparations. Generally recognised risk factors for venous thromboembolism (VTE) include a positive personal or family history (VTE in a sibling or a parent at a relatively early age), age, obesity, prolonged immobilisation, major surgery or major trauma. In case of long-term immobilisation it is advisable to discontinue the use of Visanne (in the case of elective surgery at least four weeks in advance) and not to resume treatment until two weeks after complete remobilisation.

The increased risk of thromboembolism in the puerperium must be considered.

Treatment should be stopped at once if there are symptoms or suspicion of an arterial or venous thrombotic event.

Effects on Fertility
Based on available data, ovulation is inhibited in the majority of patients during treatment with Visanne. However, Visanne is not a contraceptive.

If contraception is required a non-hormonal method should be used (e.g., condom). Based on available data, the menstrual cycle returns to normal within 2 months after cessation of treatment with Visanne.

Use in Pregnancy (Category B3)

The administration of Visanne during pregnancy is contraindicated. If pregnancy occurs during use of Visanne, use of the product must be discontinued.

The data from a limited number of cases of exposure during pregnancy suggests that dienogest does not show adverse effects on pregnancy or on the health of the foetus/newborn. To date, no significant epidemiological data has been obtained.

Preclinical data reveal no special risks on pregnancy, embryonic/foetal development, birth or development after birth for humans.

Visanne must not be administered to pregnant women because there is no data to suggest a need to treat endometriosis during pregnancy.

Pregnancies that occur among users of progestogen-only preparations used for contraception (e.g. minipill) are more likely to be ectopic than are pregnancies among users of combined oral contraceptives. Therefore, in women with a history of extrauterine pregnancy or an impairment of tube function, the use of Visanne should be decided on only after carefully weighing the benefits against the risks.

Patients are advised to use non-hormonal methods of contraception (e.g. barrier contraception such as condom) to prevent unwanted pregnancies.

Oral treatment of rats and rabbits with dienogest during organogenesis caused an increase in post implantation loss at systemic exposure levels (based on *AUC)* similar to that anticipated clinically. No teratogenicity was evident in either species at systemic exposure levels up to ten-fold higher than that expected at the clinical dose, based on *AUC.* Oral treatment of rats with dienogest during late pregnancy and lactation was shown to impair fertility in the offspring at maternal systemic exposure levels (based on *AUC)* approximately one-third of that anticipated clinically.

Changes in bleeding pattern

Visanne treatment affects the menstrual bleeding pattern in the majority of women (see ADVERSE EFFECTS). Uterine bleeding, for example in women with adenomyosis uteri or uterine leiomyomata, may be aggravated with the use of Visanne. If bleeding is heavy and continuous over time this may lead to anaemia (severe in some cases). In the event of anaemia, discontinuation of Visanne should be considered.

Chloasma

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking Visanne.

Osteoporosis

Currently, long-term data on bone mineral density (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). 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 Safety).

Other
Patients who have a history of depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Visanne generally does not appear to affect blood pressure in normotensive women. However, if a sustained clinically significant hypertension develops during the use of Visanne, it is advisable to withdraw Visanne and treat the hypertension.

Recurrence of cholestatic jaundice and/or pruritus which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of Visanne.

Persistent ovarian follicles (often referred to as functional ovarian cysts) may occur during the use of Visanne. Most of these follicles are asymptomatic, although some may be accompanied by pelvic pain.
Each Visanne tablet contains 63 mg of lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption who are on a lactose free diet should consider the amount contained in Visanne.

Diabetes
Visanne may have a slight effect on peripheral insulin resistance and glucose tolerance. Diabetic women, especially those with a history of gestational diabetes mellitus, should be carefully observed while taking Visanne.

Use in Lactation
Visanne should not be used during lactation. It is unknown if dienogest is excreted in human milk. Data in animals have shown excretion of dienogest in rat milk.

A decision must be made whether to discontinue breast feeding or to abstain from Visanne therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Paediatric use
Visanne is not indicated in children prior to menarche. The safety and efficacy of Visanne in adolescents (menarche to 18 years) has not yet been established.

Geriatric use
There is no relevant indication for the use of Visanne in the geriatric population.

Patients with hepatic impairment
Visanne is contraindicated in patients with present or past severe hepatic disease.

Patients with renal impairment
There is no data suggesting the need for a dosage adjustment in patients with renal impairment.

Carcinogenicity
A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using oral contraceptives (OCs), mainly oestrogen-progestogen preparations. The excess risk gradually disappears during the course of the 10 years after cessation of combined oral contraceptives (COC) use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. The risk of having breast cancer diagnosed in progestogen-only pill users is possibly of similar magnitude to that associated with COC, i.e., the pill. However, for progestogen-only preparations, the evidence is based on much smaller patient numbers and so is less conclusive than for COCs. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in OC users, the biological effects of OCs or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of hormonal substances such as the one contained in Visanne. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. A hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking Visanne.

Long-term studies in rats and mice with dienogest showed increased incidences of pituitary adenomas, fibroepithelial mammary tumours, stromal polyps of the uterus and malignant lymphoma, at doses corresponding to exposure levels about 10 times that anticipated at the maximum recommended clinical dose, based on area under the plasma concentration time curve (AUC). Similar tumours have been shown to develop with other oestrogenic/ progestogenic compounds. The tumours are thought to result from marked species differences in the optimal oestrogen:progestogen ratio for reproductive function. Dienogest showed no tumour promotion activity in the rat

liver foci assay at exposure levels corresponding to >100 times the estimated human exposure at the clinical dose, based on AUC.

Genotoxicity
Dienogest did not exhibit any evidence of genotoxic potential in assays for gene mutations in bacterial or mammalian cells, *in vitro* and *in vivo*

Medical Examination
A complete medical history and physical and gynaecological examination should be taken prior to the initiation or reinstitution of Visanne, guided by the CONTRAINDICATIONS and PRECAUTIONS, and should be repeated at least annually during the use of Visanne. The frequency and nature of these assessments should be adapted to the individual woman but should generally include special reference to blood pressure, breasts, abdomen and pelvic organs and should also include cervical cytology.

Interactions with other medicines
Individual enzyme-inducers or inhibitors (CYP3A4)

Progestogens, including dienogest are metabolised mainly by the cytochrome P450 3A4 system (CYP3A4) located both in the intestinal mucosa and in the liver. Therefore, inducers or inhibitors of CYP3A4 may affect the progestogen drug metabolism.

An increased clearance of sex hormones due to enzyme induction may reduce the therapeutic effect of Visanne and may result in undesirable effects e.g., changes in the uterine bleeding profile.

A reduced clearance of sex hormones due to enzyme inhibition may increase the therapeutic effect of Visanne and may result in undesirable effects.

- Substances with enzyme-inducing properties

Interactions can occur with drugs (e.g. phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin, nevirapine and products containing St. John's Wort) that induce microsomal enzymes (e.g., cytochrome P450 enzymes) which can result in increased clearance of sex hormones. Maximum enzyme induction is generally not seen for 2-3 weeks but may then be sustained for at least 4 weeks after the cessation of therapy.

The effect of the CYP3A4 inducer rifampicin was studied in healthy postmenopausal women. Co-administration of rifampicin with oestradiol valerate/dienogest tablets led to significant decreases in steady state concentrations and systemic exposures of dienogest. The systemic exposure of dienogest at steady state, measured by AUC (0 – 24h), was decreased by 83%.

- Substances with enzyme-inhibiting properties

Known CYP3A4 inhibitors like azole antifungals (e.g., ketoconazole, itraconazole, fluconazole), cimetidine, verapamil, macrolides (e.g., erythromycin, clarithromycin and roxithromycin), diltiazem, protease inhibitors (e.g., ritonavir, saquinavir, indinavir, nelfinavir), antidepressants (e.g., nefazodone, fluvoxamine, fluoxetine) and grapefruit juice may increase plasma levels of progestogens and result in undesirable effects.

In a study investigating the effect of CYP3A4 inhibitors (ketoconazole, erythromycin) on the combination of oestradiol valerate/dienogest, steady state dienogest plasma levels were increased. Co-administration with the strong inhibitor ketoconazole resulted in a 186% increase of AUC (0 – 24h) at steady state for dienogest. When co-administered with the moderate inhibitor erythromycin, the AUC (0 – 24h) of dienogest at steady state was increased by 62%. The clinical relevance of these interactions is unknown.

Effects of other medicaments on Visanne

Based on *in vitro* inhibition studies, a clinically relevant interaction of Visanne with the cytochrome P450 enzyme mediated metabolism of other medicaments is unlikely.

Drug Food interactions
A standardised high fat meal did not affect the bioavailability of Visanne.

Effects of Laboratory tests
The use of progestogens may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of (carrier) proteins, e.g. lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

Effects on ability to Drive or use Machines
Not known.

ADVERSE EFFECTS

Undesirable effects are more common during the first months after start of intake of Visanne, and subside with duration of treatment. In addition to the undesirable effects listed in Section PRECAUTIONS the following undesirable effects have been reported in users of Visanne, although a causal relationship could not always be confirmed.

The most frequently reported undesirable effects during treatment that were considered at least possibly related to Visanne were headache (9.0%), breast discomfort (5.4%), depressed mood (5.1%), and acne (5.1%).

Table 1, below reports adverse drug reactions (ADRs) by MedDRA system organ classes (MedDRA SOCs). The frequencies are based on pooled data of four clinical trials including 332 patients (100.0%).

Table 1: Categorised relative frequency of women with ADRs, by MedDRA SOC, 2 mg dienogest group – based on pooled data of four clinical trials including 332 patients

System Organ Class	**Common (≥ 1/100 and < 10/100)**	**Uncommon (≥ 1/1000 and < 1/100)**
Blood and lymphatic system disorders		Anaemia (1; 0.3%)
Metabolism and nutrition disorders	Weight increased (12; 3.6 %)	Weight decreased (1; 0.3%) Increased appetite (1; 0.3%)
Psychiatric disorders	Depressed mood (17; 5.1%) Sleep disorder[I] (7; 2.1%) Nervousness (5; 1.5%) Loss of libido (5; 1.5%) Mood altered (4; 1.2%)	Anxiety (2; 0.6%) Depression (2; 0.6%) Mood swings (1; 0.3%)
Nervous system disorders	Headache (30; 9.0%) Migraine (4; 1.2%)	Autonomic nervous system imbalance (3; 0.9%) Disturbance in attention (2; 0.6%)
Eye disorders		Dry eye (1; 0.3%)
Ear and labyrinth disorders		Tinnitus (1; 0.3%)
Cardiac disorders		Unspecified circulatory system disorder (1; 0.3%) Palpitations (1; 0.3%)
Vascular disorders		Hypotension (1; 0.3%)
Respiratory, thoracic and mediastinal disorders		Dyspnoea (1; 0.3%)
Gastrointestinal disorders	Nausea (14; 4.2%) Abdominal pain[II] (12; 3.6%) Flatulence (10; 3.0%) Abdominal distension (4; 1.2%) Vomiting (4; 1.2%)	Diarrhoea (2; 0.6%) Constipation (2; 0.6%) Abdominal discomfort (2; 0.6 %) Gastrointestinal inflammation[III] (2; 0.6%)

System Organ Class	Common (≥ 1/100 and < 10/100)	Uncommon (≥ 1/1000 and < 1/100)
		Gingivitis (1; 0.3%)
Skin and subcutaneous tissue disorders	Acne (17; 5.1%) Alopecia (5; 1.5%)	Dry skin (3; 0.9%) Hyperhidrosis (2; 0.6%) Pruritus (2; 0.6%) Hirsutism (1; 0.3%) Onychoclasis (1; 0.3%) Dandruff (1; 0.3%) Dermatitis (1; 0.3%) Hair growth abnormal (1; 0.3%) Photosensitivity reaction (1; 0.3%) Pigmentation disorder (1; 0.3%)
Musculoskeletal and connective tissue disorders	Back pain (4; 1.2%)	Bone pain (1; 0.3%) Muscle spasms (1; 0.3%) Pain in extremity (1; 0.3%) Heaviness in extremities (1; 0.3%)
Renal and urinary disorders		Urinary tract infection [IV] (2; 0.6%)
Reproductive system and breast disorders	Breast discomfort [V] (18; 5.4%) Ovarian cyst [VI] (10; 3.0%) Hot flush (9; 2.7%) Uterine / Vaginal bleeding including Spotting [VII ,VIII] (5; 1.5%)	Vaginal candidiasis (3; 0.9%) Vulvovaginal dryness [IX] (3; 0.9%) Genital discharge [X] (2; 0.6%) Pelvic pain (2; 0.6%) Atrophic vulvovaginitis (1; 0.3%) Breast mass (1; 0.3%) Fibrocystic breast disease (1; 0.3%) Breast induration (1; 0.3%)
General disorders and administration site conditions	Asthenic conditions [XI] (10;3.0%) Irritability (5; 1.5%)	Oedema [XII] (2; 0.6%)

The most appropriate MedDRA term (version 11.0) to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed, but should be taken into account as well.

I Sleep disorder consists of sleep disorder (5; 1.5%), insomnia (2; 0.6%).

II Abdominal pain consists of abdominal pain (5; 1,5%), abdominal pain lower (5; 1.5 %), abdominal pain upper (2; 0.6%).

III Gastrointestinal inflammation consists of gastrointestinal inflammation (1; 0.3%), gastritis (1; 0.3%).
IV Urinary tract infection consists of urinary tract infection (1; 0.3%), cystitis (1; 0.3%)
V Breast discomfort consists of breast discomfort (11; 3.3%), breast engorgement (4; 1.2%), breast pain (3; 0.9%).
VI Ovarian cyst consists of ovarian cyst (9; 2.7%), haemorrhagic ovarian cyst (1; 0.3 %).
VII Uterine/ Vaginal bleeding including spotting consists of dysfunctional uterine bleeding (1; 0.3%), metrorrhagia (1; 0.3%), menorrhagia (1; 0.3%), uterine haemorrhage (1; 0.3%), vaginal haemorrhage (1; 0.3%).
VIII According to bleeding diaries, irregularities in menstrual bleeding occurred more often but were usually not reported as adverse drug reaction by the patients. Please refer to text below the table for further information.
IX Vulvovaginal dryness consists of vulvovaginal dryness (2; 0.6%), mucosal dryness (1; 0.3%).
X Genital discharge consists of genital discharge (1; 0.3%) and vaginal discharge (1; 0.3%).
XI Asthenic conditions consists of fatigue (6; 1.8%), asthenia (2; 0.6%), malaise (2; 0.6 %).
XII Oedema consists of oedema (1; 0.3%), face oedema (1; 0.3%).

- Uterine bleeding irregularities

Menstrual bleeding patterns were assessed systematically using patient diaries and were analysed using the WHO 90 day reference period method.

During the first reference period (i.e. first 90 days of treatment with Visanne): The following bleeding patterns were observed (n=290; 100%): Amenorrhoea (1.7%), infrequent bleeding (27.2%), frequent bleeding (13.4%), irregular bleeding (35.2%), prolonged bleeding (38.3%), normal bleeding, i.e. none of the previous categories (19.7%)[‡].

During the fourth reference period the following bleeding patterns were observed (n=149; 100%): Amenorrhoea (28.2%), infrequent bleeding (24.2%), frequent bleeding (2.7%), irregular bleeding (21.5%), prolonged bleeding (4.0 %), normal bleeding, i.e. none of the previous categories (22.8%)[‡].

Changes in menstrual bleeding patterns were only occasionally reported as adverse event by the patients (See Table 1).

DOSAGE AND ADMINISTRATION

Tablet taking can start on any day of the menstrual cycle. The dosage of Visanne is one tablet daily without any break, taken preferably at the same time each day with some liquid as needed. Tablets must be taken throughout 28 days without regard to bleeding. When a pack is finished the next one should be started without interruption.

The efficacy of Visanne may be reduced in the event of missed tablets, vomiting and/or diarrhoea (if occurring within 3-4 hours after tablet taking). In

[‡] Sums up to more than 100% because one patient may fall into more than one category at the same time, e.g. “frequent bleeding” and “irregular bleeding”.

the event of missed tablet(s), the woman should take one tablet only, as soon as she remembers, and should then continue next day to take the tablet at her usual time. A tablet not absorbed due to vomiting or diarrhoea should likewise be replaced by one tablet.

If a short acting, e.g., oral, hormonal treatment was prescribed before starting treatment with dienogest, treatment may be started on the first day of menstrual bleeding after cessation of treatment.
If a long-acting, i.e. injectable, hormonal treatment was administered before stating treatment with dienogest then dienogest may be started

There is no experience with Visanne treatment for more than 15 months in patients with endometriosis.

OVERDOSAGE

Acute toxicity studies performed with Visanne did not indicate a risk of acute adverse effects in case of inadvertent multiple daily therapeutic dose. There is no specific antidote. 20 - 30 mg dienogest per day (10 to 15 times higher dose than in Visanne) over 24 weeks of use was well tolerated.

PRESENTATION AND STORAGE

Visanne tablets are contained in blister packs. Each blister contains 14 white tablets containing dienogest 2 mg.

Carton containing blister packs of 2 x 14, 6 x 14 or 12 x 14 tablets. Not all pack sizes may be marketed.

Shelf life is 5 years when stored below 25°C.

NAME AND ADDRESS OF SPONSOR

Made in Germany for:

Bayer Australia Ltd
ABN 22 000 138 714
875 Pacific Highway
PYMBLE NSW 2073

POISONS SCHEDULE

S4: Prescription Only Medicine

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Approved Product Information for VISANNE is available on the TGA web site www.tga.gov.au