COLLEGE TER BEOORDELING VAN GENEESMIDDELEN - MEDICINES EVALUATION BOARD

PUBLIC ASSESSMENT REPORT

Climodien, coated tablets 2/2 mg RVG 24830

International Non-proprietary Name (INN) dienogest + estradiol valerate

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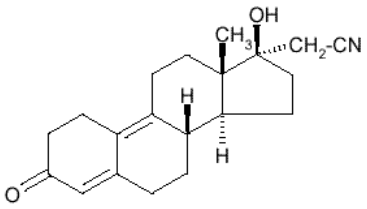
Report version: 1st NPAR, original Date 2002-01-17

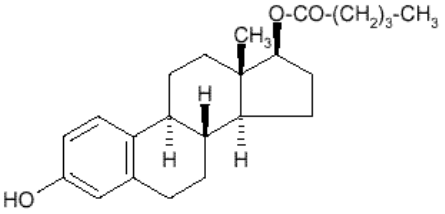
GENERAL INFORMATION

Active substance: dienogest 2 mg/tablet
estradiol valerate 2 mg tablet

Structural formulas:



dienogest



estradiol valerate

Pharmacotherapeutic group:	Progestagens and estrogens
ATC code:	G03FA15
Pharmaceutical dosage form	coated tablets
Route of administration:	oral
Therapeutic indication:	Hormone replacement therapy for estrogen deficiency symptoms in women who are at least one year postmenopausal and who still have their uterus
Prescription information:	prescription only
Marketing Authorisation Holder:	Schering, Weesp, The Netherlands
Date of first application (national):	1999-09-28
Application type/legal basis:	Directive 65/65/EEC, Article 4.8 (a)

Date of authorisation: 2000-12-13
Completion of Mutual Recognition Procedure (Directive 75/3198/EEC): 2001-05-08

Countries recognising Dutch assessment: Austria, Belgium, Denmark, France, Germany, Greece, Iceland, Luxembourg, Norway, Portugal, Spain and Sweden.

ABSTRACT

On 13-12-2000, the Medicines Evaluation Board in the Netherlands issued a marketing authorisation for the medicinal product Climodien, which contains a fixed combination of
2 mg estradiol valerate and 2 mg dienogest. For The Netherlands, the progestagen dienogest is a new active substance.
The approved indication is “hormone replacement therapy for estrogen deficiency symptoms in women who are at least one year post menopausal and who still have their uterus”. An annotation to the therapeutic indication is that experience with the product is limited in women older than 65 years.

The treatment with continuous combined HRT is commonly restricted to those women who are 1-2 years in the postmenopausal state. The reason for this restriction is that women who are perimenopausal, or early menopausal, may still have clinically relevant residual production of estradiol. In this situation, the risk for irregular bleeding (breakthrough bleeding) is very high.

The dose recommendation is one tablet daily, for continuous treatment. The Summary of Product Characteristics (SPC, part IB1 of the dossier) describes detailed conditions for the use of this product. The SPC is an annex to this Public Assessment Report.

Climodien is available as a conventional coated tablet and contains common excipients. In the commercial package the product has a stability of 2 years, when stored not above 25°C.

In pre-clinical experiments, dienogest shows less (10-30 X) affinity to the progesterone receptor than other synthetic progestagens and progesterone itself. Compared with levonorgestrel, anti-progestational as well as estrogenic properties of dienogest are stronger. Dienogest has low androgenic effects and clear anti-androgenic properties. Plasma protein binding in humans is 93-94%. The metabolism of dienogest is complex. CYP3A4 has been identified as the predominant isoenzyme in the metabolic pathway. At least nine metabolites can be isolated from urine. All metabolites observed in humans appear in test animals also. Toxicological studies with dienogest do not show any remarkable effects. The pharmacological and toxicological properties of estradiol valerate are known from the literature and will not be discussed in this report.

Clinical trials investigated the efficacy and safety of Climodien use with the requested indication. The study design put an emphasis on the clinical performance of dienogest in the recommended dose in the prevention of endometrial hyperplasia. Adequate protection of the endometrium has been demonstrated according to the

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recommendations of the CPMP 'Points to consider in Hormone Replacement Therapy' (CPMP/EWP/021/97). The efficacy of estradiol valerate 2 mg in the treatment of postmenopausal symptoms of estrogen deficiency is since long established. The presented extensive clinical data in this dossier have re-established the efficacy, which appeared not to be attenuated by the addition of dienogest 2 mg. Double-blind comparison with Kliogest (estradiol 2 mg + norethisterone acetate 1 mg) indicated comparable efficacy and adverse event pattern. HRT is associated with an increased risk for venous thrombosis and breast cancer. Due to the limited study population in the clinical studies, the registration dossier does not allow conclusions regarding the relative incidence of these rare events. The marketing authorisation holder has made the commitment to perform a post-marketing study, in which, among others, the incidence of venous thrombosis will be followed.

The presented clinical documentation does not allow any statements on possible clinical advantages of dienogest over approved progestagens in HRT.

The SPC is adapted to the latest European opinions on the use of hormone replacement therapy.

The Medicines Evaluation Board, on the basis of quality, efficacy and safety data submitted, considered that Climodien can be consistently produced with sufficient quality.
Efficacy for the therapeutic indication as well as safety has adequately been shown.

SAMENVATTING

Op 13-12-2000 heeft het College ter beoordeling van geneesmiddelen Climodien geregistreerd. Dit geneesmiddel bevat per tablet de vaste combinatie van 2 mg oestradiolvaleraat en 2 mg dienogest. Het progestativum dienogest is in Nederland een nieuw werkzaam bestanddeel. De goedgekeurde indicatie is:
Hormoonsuppletietherapie (HST) bij de behandeling van symptomen van oestrogeen-deficiëntie bij vrouwen die op zijn minst een jaar postmenopauzaal zijn en bij wie de baarmoeder niet verwijderd is. Deze restrictie is gebaseerd op het feit dat bij perimenopauzale – en vroeg-menopauzale vrouwen nog een klinisch relevante oestrogeenproductie kan bestaan. Daardoor is bij deze vrouwen de kans op irregulier bloedverlies (doorbraakbloedingen) bij gebruik van een continue gecombineerd HRT preparaat erg groot. Bij de indicatie is de kanttekening geplaatst dat de ervaring beperkt is bij de behandeling van vrouwen die ouder zijn dan 65 jaar.

De aanbevolen dosering is één tablet per dag, voor continue behandeling. De gedétailleerde voorwaarden voor het gebruik van het geneesmiddel staan beschreven in de Samenvatting van de kenmerken van het product (deel IB1 van het registratiedossier). Deel IB1 is bij dit rapport gevoegd.

Climodien is beschikbaar als gewone omhulde tablet en bevat gangbare hulpstoffen. In de handelsverpakking is het product 2 jaar houdbaar als het niet boven 25 °C wordt bewaard.

Bij preklinisch onderzoek blijkt dienogest een lagere (10-30X) affiniteit voor de progesteronreceptor te hebben dan andere synthetische progestagenen en progesteron zelf. In vergelijking met levonorgestrel zijn zowel de anti-progestagene en oestrogene activiteit van dienogest groter. Dienogest heeft een lage androgene activiteit en duidelijke anti-androgene eigenschappen. De binding aan menselijk plasma-eiwit is 93-94%. Het metabolisme van dienogest is ingewikkeld. CYP3A4 is het voornaamste enzym in de metabole route. In de urine zijn tenminste 9 metabolieten aangetoond. Alle metabolieten die bij mensen zijn aangetoond komen ook voor bij de geteste diersoorten. Toxicologisch onderzoek laat geen bijzonderheden zien. De farmacologische en toxicologische eigenschappen van estradiolvaleraat zijn bekend uit de literatuur en worden niet besproken in dit rapport.

De effectiviteit en veiligheid van Climodien bij de gevraagde indicatie en de aanbevolen dosering zijn aangetoond met klinisch onderzoek. De nadruk lag hierbij op het klinisch gedrag van dienogest bij de preventie van endometriumhyperplasie. De bescherming van het endometrium was voldoende volgens de CPMP-aanbeveling "'Points to consider in Hormone Replacement Therapy' (CPMP/EWP/021/97). De werkzaamheid van estradiolvaleraat 2 mg bij postmenopausale symptomen van oestrogeen deficiëntie is reeds lang bekend. De uitgebreide gegevens uit het dossier van Climodien stellen deze werkzaamheid opnieuw vast. Dienogest schijnt het effect van estradiolvaleraat niet af te zwakken.

In een dubbelblind vergelijkend onderzoek waren de werkzaamheid en het bijwerkingenpatroon van Climodien vergelijkbaar met die van Kliogest (estradiol 2 mg + norethisteronacetaat 1 mg). Hormoonsuppletietherapie wordt in verband gebracht met een toegenomen risico van veneuze trombose en borstkanker. Door de beperkte omvang van de patiëntenpopulatie in het onderzoek voor geneesmiddelregistratie kan geen uitspraak worden gedaan over het relatieve voorkomen van deze zeldzame bijwerkingen. De registratiehouder heeft de toezegging gedaan om "post marketing"-onderzoek uit te voeren waarbij het vóórkomen van onder andere veneuze trombose wordt vastgesteld.

Op basis van het klinische onderzoek kan geen uitspraak worden gedaan over een mogelijk klinisch voordeel van dienogest boven andere progestagenen voor HST.

De samenvatting van de kenmerken van het product (deel I B1 van het registratiedossier) is aangepast aan recente Europese standpunten over HST.

Het College ter beoordeling van geneesmiddelen heeft op basis van de overgelegde gegevens geconstateerd dat Climodien met constante, voldoende kwaliteit kan worden geproduceerd. De werkzaamheid en veiligheid bij de gestelde indicatie zijn voldoende bewezen.

SCIENTIFIC DISCUSSSION

INTRODUCTION

Climodien is a continuous combined hormone replacement therapy (HRT) for oral use in women with an intact uterus. The product consists of a fixed combination of two active ingredients, estradiol valerate 2 mg and dienogest 2 mg. For The Netherlands, dienogest, a derivative of nortestosterone, is a new progestagen. Dienogest is the active ingredient of two oral combined contraceptives that are marketed only in Germany in 1991 and 1995, respectively Certostat (ethinyl estradiol 50 µg + dienogest 2 mg) and its successor Valette (30 µg ethinyl estradiol + dienogest 2 mg). The rationale for the development of a new progestagen like dienogest was to have a progestagen with strong anti-estrogenic and progestational effect and no androgenic effect.

The estrogenic component, estradiol valerate, is a prodrug of estradiol. The esterification leads to a greater bioavailability of estradiol. Estradiol valerate as monotherapy is since long registered for estrogen replacement therapy under the name of Progynova and is also a component of a number of combined HRT's.

The therapeutic indication for Climodien is: hormone replacement therapy for estrogen deficiency symptoms in women who are at least one year postmenopausal and who still have their uterus. Additional claims proposed for inclusion under Pharmacodynamic effects of the SPC included a positive effect on postmenopausal sleeping disorders and a statement on direct action of estrogens on the vasculature, that is not diminished by the addition of dienogest. These claims could not be allowed. The dose recommendation is one tablet daily.

In The Netherlands, several oral HRT preparations are registered containing a fixed combination of both estrogens and progestagens for continuous combined use in women with intact uterus who are 1-2 years in the postmenopausal state:

Kliogest	Estradiol 2 mg + norethisterone acetate 1 mg
Activelle	Estradiol 1 mg + norethisterone acetate 0.5 mg
Premelle 5/10	Conjugated estrogens/medroxyprogesterone 0.625mg/5mg; 1, 25mg/10mg
FemHRT 1/5, 1/10	Ethinyl estradiol/norethisterone acetate 5µg/1 mg; 10µg/1mg
Indivina	Estradiol valerate/medroxyprogesterone 1mg/2.5mg; 1/mg/5mg; 2mg/5 mg

Additionally, one transdermal patch with a fixed combination of estrogens and progestagens for continuous combined use is registered in The Netherlands (Estalis).

The treatment with continuous combined HRT is commonly restricted to those women who are 1-2 years in the postmenopausal state. This restriction is made because women who are perimenopausal or early menopausal may still have clinically relevant residual production of estradiol. In this situation, the risk for irregular bleeding (breakthrough bleeding) is very high.

The clinical part of the registration dossier consisted of six pharmacodynamic studies of which one investigated pharmacodynamic effects related to the therapeutic indication, nine pharmacokinetic studies and six phase II/III clinical studies. The phase

III studies were carried out in conformity with the CPMP 'Points to consider in Hormone Replacement Therapy' (CPMP/EWP/021/97).

CHEMICAL-PHARMACEUTICAL ASPECTS

Composition

Climodien consist of a combination of the new active substance dienogest (2 mg) and estradiol valerate (2 mg) Climodien is available as a conventional coated tablet and contains common excipients. The excipients used in the tablet core are lactose monohydrate, magnesium stearate, potato starch gelatine, and talc.
The excipients used in the tablet coating are: sucrose, glucose liquid, calcium carbonate, polyvidone 25000, macrogol 35000, carnauba wax, titanium dioxide (E171) and ferric oxide red (E172).

The commercial package is a polyvinylchloride/aluminium blister pack containing 28 coated tablets. The blister packs are available in cartons containing 28 or 3 x 28 tablets.

Product development

The objective of the pharmaceutical development was to obtain a solid oral dosage form with direct release characteristics and good mechanical-, chemical-, and photochemical stability. Furthermore, the objective was to use common excipients and common production techniques.

Manufacturing

A standard pharmaceutical tabulating process comprises the tablets. The process is documented and validated sufficiently also with respect to the content uniformity of the tablets. The results of the in-process controls and the retrospective analysis of several batches of the finished product and granulation mixtures showed this.

Starting materials, active substances and excipients

Dienogest
Dienogest is not described in any pharmacopoeia. The quality of dienogest is monitored by specifications on appearance, identity (IR-spectrometry, HPLC, DLC, specific optical rotation), particle size, colour of a solution, assay, related substances, sulphated ash, water, heavy metals and residual solvents. Polymorphism does not occur with this active substance. De authorisation holder guarantees the monograph in which sufficient specifications are included. The scientific documentation in the dossier, including the full synthetic pathway, shows that the specifications included in the monograph are suitable for the control of the substance. The specifications for related substances are also acceptable from a toxicological point of view.

Estradiol valerate
The quality of estradiol valerate is monitored by specifications on appearance, identity (IR-spectrometry, specific optical rotation), particle size, colour of a solution, assay, related substances, loss on drying, free acid, and residual solvents.
Estradiol valerate does not show polymorphism. The authorisation holder guarantees the monograph in which sufficient specifications are included. The specifications are

derived from the draft monograph for the European Pharmacopea as published in Pharmeuropa (Vol. 11, No. 3, Sept. 1999, Page 538 – 539. The scientific documentation in the dossier, including the full synthetic pathway, shows that the specifications included in the monograph are suitable for the control of the substance. The specifications for related substances are also acceptable from a toxicological point of view.

Excipients
All the excipients used in the manufacturing of the drug product are of European Pharmacopoeia quality, except ferric oxide red which is of French Pharmacopoeia quality.

Specifications and control methods for the finished product

The main control parameters for this product are the identification of both active substances and the colouring agents, the assay of the active ingredients, the specification for impurities, the dissolution rate, and the content uniformity. The specifications for the finished product are suitable with respect to both quality and safety. Batch analysis results of various batches show that the product meets the specifications set.

Stability

Stability of the finished product
The storage period for the finished product is two years, when stored not above 25°C, in the former described commercial package. The shelf life of two years was granted based on an ongoing stability study. All stability studies are in accordance with the ICH/CPMP-Guidelines. The end- of-shelf-life specifications for the finished product are adequate with respect to both quality and safety.

PRECLINICAL PHARMACOLOGICAL AND TOXICOLOGICAL ASPECTS

Climodien is a combined hormone replacement product contains 2 mg estradiol valerate and 2 mg dienogest as active ingredients. Dienogest is a new active substance. Estradiol valerate is a well-known substance already on the market in the Netherlands. Its properties will not be discussed in this report.

Pharmacodynamics

Dienogest, a nortesterone derivative, is a new synthetic progestogen. Relative binding of dienogest to the progesterone receptor is 10 to 30 times less than progesteron or other synthetic progestogens. Binding to the glucocorticoid and androgen receptor is low and to the mineralocorticoid receptor and to the estrogen receptor negligible. Other studies have shown that dienogest does not bind to the sex hormone binding globulin (SHBG) and the corticoid binding globulin (CBG). The strong *in vivo* progestational activity of dienogest in rabbits as compared to other progestagens does not correlate with its relatively low affinity to progesterone receptor. The rabbit seems to be more sensitive to the progestational activities of dienogest than the rat or mouse. The high *in*

vivo activity despite relatively low receptor binding might be explained by the higher volume of distribution and a longer residence time in rabbits as compared to other species.

In animal experiments, Dienogest as compared with levonorgestrel has stronger anti-progestational and stronger estrogenic properties. Dienogest has a 10-30 times lower androgenic potency as compared with 3-keto-desogestrel and has clear anti-androgenic properties with a potency of 40 % as compared with cyproterone acetate. Dienogest has no mineralocorticoid effects and has no glucocorticoid properties. No pharmacodynamic studies were performed with the proposed combination dienogest/estradiol valerate.

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

Pharmacokinetics

Dienogest
Dienogest was rapidly absorbed after oral administration. Absolute bioavailability is high. Plasma protein binding was 86-99% in rats, 87-93% in dogs, 91-92% in baboons and 93-94% in humans. The difference in free fraction in humans compared to other species cannot be ignored. The volume of distribution among species ranged from 0.6 l/kg in rats and dogs to 3.2 l/kg in rabbits. Dienogest was rapidly distributed in female rats. In monkey and human mainly unchanged dienogest was found in plasma, while in rat plasma besides unchanged dienogest some metabolites were found.
In monkey and human mainly unchanged dienogest was found in plasma, while in rat plasma besides unchanged dienogest some metabolites were found, clarifying species differences in dynamics. Experiments have shown that the main metabolite in rat plasma was responsible for the estrogenic effects seen in this species.

Hydroxylation plays the major role in metabolism of dienogest in all species investigated. Metabolites were excreted as free steroids, glucuronides and sulphates. CYP3A4 was identified as the predominant isoenzyme. Dienogest does not inhibit CYP1A2, CYP2D6, CYP2E1, CYP3A4, CYP2C9 and CYP2C19. All metabolites observed in human also occurred in the test animals. Data on interactions and enzyme induction are lacking, but clinical studies showed that pharmacokinetics of dienogest is unaffected by co-administration of estradiol valerate and vice versa. Dienogest was rapidly eliminated from plasma with $t_{1/2}$ of 5-9 hrs. Based on the plasma concentration versus time curve in rats and mice there was evidence for entero-hepatic circulation.

Toxicology

Single dose toxicity
At high oral doses in mice, central depression was the main clinical sign of toxicity.

Repeated dose toxicity
In all four species (mouse, rat, dog, monkey) predominantly the expected pharmacological effects on the reproductive system were found. In all four species (mouse, rat, dog, monkey) predominantly the expected pharmacological effects on the reproductive system were found. Furthermore, effects were found on liver (increase liver weight, fat deposition) and on serum parameters (cholesterol, blood clotting

factors, alkaline phosphatase) and red blood parameters (decrease in erythrocyte and hematocrit; increase in thrombocytes)

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

Mutagenic potential
On basis of the presented studies, it can be concluded that dienogest has no mutagenic potential.

Carcinogenic potential
Dienogest shows no unexpected effects in carcinogenicity-tests. The observed tumour types were indicative for the (weak) estrogenic properties of dienogest.
It is concluded that dienogest has no carcinogenic potential in rodents which is relevant to human health.

CLINICAL ASPECTS

The following abbreviations appear in this chapter:

HRT	hormone replacement therapy
EV	estradiol valerate
DNG	dienogest
LNG	levonorgestrel
NETA	norethisterone acetate
FSH	follicle stimulating hormone
SHBG	sex hormone binding protein
Climodien 2/3	ethinyl estradiol 30 µg + dienogest 3 mg.

The clinical dossier included 6 pharmacodynamic studies of which one investigated pharmacodynamic effects related to the therapeutic indication**,** 9 pharmacokinetic studies and 6 phase III clinical studies.

Pharmacokinetics

Estradiol valerate is hydrolysed to estradiol within the intestine and subsequently absorbed in the gut wall. The pharmacokinetics of estradiol and its main metabolite estrone are well known and investigated thoroughly in the literature. In two multiple dose studies, the pharmacokinetics of estradiol and estrone are investigated with and without co-administration with dienogest. No bioavailability study is submitted in which the pharmacokinetics of estradiol from Climodien is compared with an already registered product.

Nine studies elucidate the pharmacokinetics of dienogest : three bioavailability studies; two single dose studies with ^{3}H-labelled dienogest; three multiple dose studies and one dose proportionality study.

Absorption

Bioavailability
The absolute bioavailability of dienogest was estimated in a study with 20 healthy male volunteers. Compared were doses of 2 mg/subject after intravenous and oral (film coated tablet) administration under fasting conditions. Results indicated the absolute bioavailability of dienogest to be 90.5%, with a confidence interval of 86% - 95%.

The relative bioavailability of dienogest with or without co-administration of estradiol valerate was estimated in a crossover study. Single doses were administered orally after overnight fast as 2 mg dienogest tablets or as a 2 mg DNG + 2 mg EV film coated tablet. This study clearly indicated that co-administration of estradiol valerate does not affect the bioavailability of dienogest. . The residual coefficients of variation were small, indicating a small intra-individual variability in the pharmacokinetics of dienogest.

The bioavailabilities of dienogest and estradiol were compared after administration of two tablets with 2 mg EV + 2 mg DNG, two tablets 2 mg EV + 3 mg DNG and a microcrystalline suspension of 4 mg EV + 6 mg DNG..
The three formulations are bioequivalent with respect to the extent of absorption. In comparison with the suspension, the relative bioavailability of estradiol and dienogest from the tablet with 2 mg DNG were 101%.

Influence of food
The influence of a high- fat breakfast on the bioavailability of dienogest from a tablet formulation with 2 mg dienogest was investigated. According to the results of that study, no influence of food was detected on the rate and extent of absorption. With respect to estradiol valerate, the influence of food has not been investigated separately. As food intake was not restricted in clinical efficacy studies, and efficacy was apparent , the possible influence of food is not considered relevant. Concerning estradiol, it is well known from the literature that the influence of food can vary from –30% to +30%. These changes may only be of minor clinical relevance with the claimed indication.
The influence of food on the bioavailability of dienogest and estradiol valerate together from Climodien is not fully elucidated. However, the clinical relevance of probably small changes is questionable.

Distribution

Drug binding
Plasma protein binding was assessed in vitro by equilibrium dialysis. The plasma protein binding was approximately 78 %. Testosterone was not displaced from its plasma protein binding by dienogest. Dienogest does not bind to SHBG, so increasing SHBG as consequence of estradiol administration will not influence the pharmacokinetics.

Metabolism and excretion

The metabolic profile of dienogest is very complicated. In a submitted study a series of metabolites has been isolated from urine Principal pathways of dienogest biotransformation are:

- hydroxylation;
- introduction of additional double bonds (originated possibly from dehydration of hydroxylated compounds;
- aromatisation of the A-ring;
- elimination of nitrogen from the 17α-side chain;
- hydroxylation and reduction of the oxo group or,
- hydrogenation of a double bond and reduction of the oxo-group or/and,
- hydrogenation of a double bond.

At least nine metabolites were isolated from the fraction of free steroids in urine, however, no quantitative data were submitted.

Preclinical data show dienogest to be metabolised by hepatic microsomes and hepatocytes. Cytochrome P450 was involved in the metabolism of dienogest. In humans the aromatic dienogest, an important metabolite in rats, was only identified in urine in one study, and not detected in two other studies. There is no good explanation for this difference. The metabolites probably do not contribute to the effects of dienogest in a relevant way. Studies with ^{3}H-labeled dienogest show that the metabolites are eliminated with a half-life of about 20 hours.

Pharmacokinetics after single dose

^{3}H-labeled dienogest was administered as single oral dose (0.1 mg/kg) to five health female volunteers In plasma the pharmacokinetics of total radioactivity and dienogest was estimated.

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

The results demonstrated that the concentration of total radioactivity is nearly two times that of dienogest. The clearance of the metabolites is slower than then of the parent compound. All studies after single dose show comparable results.

Dose proportionality

The linearity of the pharmacokinetics of dienogest was demonstrated in the range of 1 to 8 mg in healthy women.

Pharmacokinetics at steady state

From the studies in steady state it could be concluded that after multiple doses the pharmacokinetics of dienogest are not different and that there is no time dependency. The accumulation factor based on AUC_{0-24h} data is about 1.2. The variability measured in the estradiol concentrations was high as expected.

Interactions

Ín studies in which different amounts of estradiol and dienogest were co-administered dienogest did not influence the pharmacokinetics of estradiol.
Nifedipine was administered without dienogest and after treatment for 21 days with Certostat (30 µg ethinyl estradiol and 2 mg dienogest). No differences were found between the two treatments with nifedipine, indicating that dienogest does not affect CYP 3A4 metabolic system. This is in conformity with pre-clinical studies.

Pharmacokinetics in special populations

Patients with impaired renal function
About 63% of the dose administered is excreted by urine in the first 48 hours upon administration of dienogest from which 20% as unconjugated steroids and 1% unchanged. A statement that pharmacokinetics of Climodien is not investigated in patients with renal insufficiency was added to section 5.2 (Pharmacokinetic properties) of the SPC. A standard warning concerning patients with severe renal insufficiency is mentioned in section 4.4 Special warnings and precautions for use.

Patients with hepatic impairment
No studies in patients with hepatic impairment were submitted. It is stated that Climodien is contra-indicated in patients with "acute or chronic liver disorder resulting in unresolved liver function disturbances". Therefore, it should not be administered to patients with hepatic insufficiency.

Elderly
The pivotal pharmacokinetic studies (single and multiple dose studies) and clinical studies are conducted in postmenopausal women aged 45 – 75 years. As the product is intended for this population, no other data is required.

Clinical pharmacodynamics and efficacy trials

One clinical phase II study, one phase II/III study and four phase III studies were performed. All studies investigated efficacy in the treatment of postmenopausal symptoms, but this was a primary efficacy parameter in only one study. The clinical program especially focussed on the safety of Climodien and endometrial efficacy of dienogest. In this program, the double blind comparative study versus Kliogest was pivotal. This study was followed by an open extension of two years in which all women were treated with Climodien. An overview of the clinical studies is presented below.

Overview of clinical studies

Study	Design/ Duration	Treatment	Reference	Efficacy parameters*
JPH04092 Germany 1993-95	O, R, C, P 6 cycles phase II/III Dose-finding	2mgEV/0.5mg DNG (n=25) 2mgEV/1mg DNG (n=26) 2mgEV/2mg DNG(n=24) 2mgEV/3mg DNG (n=22) 2mgEV/4mg DNG(n=23)		**Endometrial histology;** Bleeding pattern; Change in hot flushes, vaginal atrophy, sleeping disorders etc.; Lipid metabolism
JPH05295 Germany, France, Czech Republic Switzerland 1996-98	O, NC 12 x 4 weeks follow-up of 6 cycles Phase III	2mgEV/2mg DNG (n=1501)		**Frequency/ severity of AEs;** Bleeding pattern; Endometrial thickness; Kupperman index; Lipid metabolism; Frequency + severity hot flush; Mammography
JPH01093 Germany 1995-98	DB, R, P 12 months Phase III	2mgEV/2mg DNG (n=199) 2mgEV/3mg DNG (n=186)	Kliogest 2mgE/1mg NETA (n=196)	**Endometrial histology;** **Kupperman index;** Hot flushes intensity, other postmenopausal symptoms; Endometrial thickness; Bleeding pattern; Vaginal cytology;
Study	**Design/ Duration**	**Treatment**	**Reference**	**Efficacy parameters***
JPH01093 Germany 1996-99 1st year follow-up (interim)	O, NC 1st year follow-up of DB phase of study JPH0193	2mgEV/2mgDNG (n=320)		**Endometrial histology;** **Bleeding pattern;** Lipid metabolism; Tolerability/acceptance;
JPH01093 2nd year follow-up (interim)	O, NC 2nd year follow-up of DB phase of study JPH0193	2mgEV/2mgDNG (n=235)		**Endometrial histology**
JPH04095 France 1996-97	DB, R, PC, P 6 x 4 weeks Phase III	2mgEV/3mg DNG (n=43)	Placebo (n=40)	**Haemostasis (prothrombin fragments 1 and 2);** Lipid metabolism; Carbohydrate metabolism; Kupperman index; Genito-urinary complaints;
JPH00696 Germany 1997	O, R, P 3 months Phase II	2mgEV/2mg DNG (n=29)	2mgEV (n=27)	**Urinary markers of vascular function** Menopausal symptoms
JPH01595 Austria 1995-1998	DB, R, PC 2 months Open phase follow-up 2 months	2mgEV/2mg DNG (n=16) 2mgEV/3mgDNG (n=16)	Placebo (n=15) 2mgEV (n=17)	**Nocturnal time of wakefulness** Other subjective/objective criteria for the quality of sleep and awakening; Kupperman index

*: primary variable in bold; O: open, R: randomised, C: controlled, NC: non-controlled, P: parallel, AEs: adverse events

Major inclusion/exclusion criteria
Women, who were ≤ 65 years of age (except for study JPH00696: ≤75 years), postmenopausal (adequate period/12 months of amenorrhoea or estrogen/FSH levels in the postmenopausal range of ≥ 25 mU/ml), and had a clinical indication for HRT. No lower age limit was set in most studies, with the exception of study JPH05295, in which the limit was set at 52 years.
Major exclusion criteria in all studies included the usual contra-indications for HRT, among others, hormone-related tumours, uncontrolled hypertension, thrombo-embolic- or cerebrovascular disorder. Additionally, an endometrial thickness of >12 mm, PAP of III-IV, otosclerosis, acute or chronic liver disease, liver tumours, and several other concomitant diseases (diabetes mellitus, angina pectoris, lipid disorder) that were not sufficiently controlled were considered exclusion criteria.

Endometrial protection

Phase I dose-response investigation of dienogest
Limited data suggested that the transformation dose of DNG after pre-treatment with 50 µg ethinyl estradiol is a daily dose of 0.45 mg (total dose of 6.3 mg), but the value of these data was considered questionable

Phase II dose-response
The effectiveness of dienogest in combination with 2 mg estradiol valerate (EV) in the prevention of endometrial hyperplasia was evaluated for the dose range of 0.5, 1, 2, 3 and 4 mg DNG. The primary target variable in this study was the endometrial biopsy performed after 6 months treatment. The lowest rate of bleeding was seen in those patients treated with 2 mg EV combined with 0,5 or 3 mg DNG. The highest rate occurred with the combination of 2 mg VE/4mg DNG.
During treatment with the combined preparation of 2 mg EV using 0.5, 1, 2, 3, and 4 mg DNG, 60%, 42.3%, 41.7%, 63.6%. and 39.1% remained amenorrhoeic, respectively.
In the majority of cases, bleeding was slight. No moderate or heavy bleeding was noted in the 3 mg DNG group, while it was observed relatively often in the 2 mg DNG group.
Based on the ratio atrophic/proliferative endometrium, 2, 3, and 4 mg were considered suitable for further investigation. However, when regarding the observed bleeding pattern, the 4 mg dose performed worse than the 2 and 3 mg. Therefore, 2 and 3 mg dienogest were selected for further development.

Phase III confirmative study data

Endometrial histology
The pivotal study regarding endometrial safety is the comparative study versus 2 mg EV/3 mg DNG (Climodien 2/3) and Kliogest (JPH01093) in which endometrial histology was the primary efficacy parameter. Endometrial biopsies were taken at study entry and after 1, 2 and 3 years treatment. The sample size of this study initially was calculated in order to have sufficient statistical power for an inter-group comparison of the incidence of “atrophic endometrium”. Additionally, the study was prolonged by two years without interruption of treatment in order to comply with the CPMP Points to Consider on HRT. Therefore, in the second- and third year, ***all*** patients (including those

who were treated with Climodien 2/3 and Kliogest during the first study year) received Climodien. This study is still ongoing (total treatment duration is 3 years). The already available data included a total number of 290 women in whom biopsies were obtained after one year and 191 women in whom biopsies were obtained after two years treatment with Climodien, respectively.
Endometrial tissue was classified as inadequate, atrophic, proliferative, secretory, hyperplastic, or others (features not belonging to any of the other 5 categories). Two independent pathologists, who were blinded with respect to study medication, diagnosed the biopsies. If differences occurred between the first and second pathologist, a third, independent blinded pathologist was to be consulted. Additionally, ultrasound was performed at entry and at month 3, 6 and 12 months. An overview of results, as presented in the clinical dossier, is presented in the next table:

Phase III study: endometrial histology

	Atrophic n (%)	Proliferative n (%)	Secretory n (%)	Hyperplasia n (%)	Carcinoma	Inadequate N (%)	Other[1] n (%)	Total N
Baseline								
Clim*	152	29 (15.0)	2 (1.0)	4 (2.1)		3 (1.6)	3	193
Clim 2/3	(78.8)	29 (16.0)	3 (1.7)	2 (1.1)		7 (3.9)	(1.6)	181
Kliogest	136	24 (12.7)	2 (1.1)	5 (2.7)		1 (0.5)	4	189
	(75.1)						(2.2)	
	154						3	
	(81.8)						(1.6)	
12 cycles[2]								
Clim	128	6 (4.3)	2 (1.4)			3 (2.1)	2	141
Clim 2/3	(90.7)	3 (2.4)	4 (3.4)			7 (5.9)	(1.4)	119
Kliogest	104	6 (4.4)	4 (2.9)			3 (2.2)	1	136
	(87.4)						(0.8)	
	119						4	
	(87.5)						(2.9)	
12 cycles[3]								
Clim	189	4 (1.8)	5 (2.2)		1 (0.45)	19 (8.5)	5	223
	(84.8)						(2.7)	
24 cycles[3]								
Clim	106	4 (3.4)	2 (1.7)			5 (3.4)	1(0.8)	117
	(90.6)							

1. 'Other' was defined as: features not belonging to any of the other categories; the combination of thin endometrium (<5mm) and insufficient material was regarded as atrophic endometrium
2. Corresponds to the main (double-blind) part of the study
3. The results of the 12- and 24-cycle follow-up treatment, displayed irrespective of the type of treatment in the main part of the study (first treatment year).

❖ Climodien

One case of endometrial carcinoma was diagnosed at the end of the one year follow-up in a woman pre-treated with Climodien 2/3 for one year (dienogest 3 mg instead of 2 mg). The incidence of this event and the corresponding upper limit of the 95% confidence intervals for Climodien 2/2 were calculated taking into account the different intervals of treatment (see next table):

Incidence of endometrial malignancy (endometrial hyperplasia/carcinoma)

Number of one-year biopsies	Number of events	Incidence	Upper one-sided 95% CI in %
290	1	0.34	1.63
191	0	0.00	1.46

In all other studies, endometrial biopsies were performed only in the situation of irregular bleeding or suspicious endometrial ultrasound findings (endometrial thickness of >5 mm).

Endometrial thickness
Evaluation of endometrial thickness during treatment was performed in three studies. In none of the studies the mean thickness measured at baseline significantly changed during treatment, although in the study that evaluated Climodien 2/3, the mean thickness was slightly increased. However, individual cases of increased endometrial thickness (13), with or without clinical symptoms, did occur.

Bleeding pattern
Pivotal information came from the comparative study versus Climodien 2/3 and Kliogest. The percentages of patients (study completers) without any bleeding indicated an increase in the number of patients with amenorrhoe with time. The percentage of women with amenorrhoea at 12 months treatment was 85% for Climodien versus 81% for Kliogest. On average, there were 30 bleeding days with Climodien 2/2, 41 bleeding days with Climodien 2/3 and 32 bleeding days with Kliogest over 12 months treatment. Additional bleeding data from the large uncontrolled study suggested an initial increase in bleeding that is highest in the second treatment cycle after which the frequency and severity of bleedings diminished with time.

Treatment of postmenopausal symptoms of estrogen deficiency
Data from the pivotal comparative study indicated the efficacy of Climodien to be comparable with that of noted for Kliogest (estradiol 2 mg + norethisterone acetate 1 mg). These efficacy of Climodien in this indication was additionally supported by the outcome of the studies, in which treatment of climacteric symptoms was considered a secondary efficacy parameter.

Nocturnal time of wakefulness
Results of one study that investigated the efficacy of Climodien 2/2 and Climodien 2/3 on postmenopausal sleep disorders versus estradiol valerate alone or placebo reported a non significant decrease in nocturnal wakefulness time during treatment with Climodien.

Safety

The overall safety analysis included 1,834 women exposed to Climodien.

Patient exposure

The following table provides an overview of the number of patients treated and the duration of treatment with Climodien:

Study	N (enrolled)	6 months	1 year	18 months	2 years	3 years
JPH04092	24	16				
JPH05295	1501	1343	1171	121		
JPH01093 main part	199	161	146	116	95	42
JPH01093 follow-up part	320	316	290	260	295	-
Total	2044	1836	1607	497	330	42

Adverse events

Two deaths were documented, which both were considered not related to the study drug (non-operable carcinoma of the biliary duct after 5 months of Climodien treatment, lethal car-accident of a patient on Kliogest). A total of 649 women withdrew from the studies of whom 368 withdrew due to an AE. A total of 116 serious adverse events were documented. Thirty-two were considered related to treatment with Climodien 2/2 or 2/3, of which bleeding problems were most frequently reported.

The most frequently (≥ 2%) reported adverse events, which by the investigators were assessed as related to Climodien included (in order of their frequency):

breakthrough bleeding/metrorrhagia (22.9%), mastalgia (13.2%), headache (5.5%), hypertension/aggravated hypertension (3.7%), thrush (2.6%), migraine (2.3%), increase in endometrial thickness (2.2%) and weight increase (2.1%). In the comparative study versus Climodien 2/3 and Kliogest, the most frequently (≥1%) reported adverse events with possible relationship to study medication did not indicate clear differences between treatment groups.

Specific safety issues

Breast cancer

During treatment, 9 women were diagnosed as having breast cancer. One case of breast carcinoma was diagnosed 3.5 months after the final study visit. According to the investigators, one of the cases was considered possibly related to study treatment (Climodien 2/3), the other eight cases were assessed as unlikely and in one case as not-related. Six of the women had a history of mammary findings already at baseline. Six of these women had previous hormone replacement therapy.

Thrombosis

In the course of the studies, seven venous thromboembolic disorders in 6 patients have been reported. In several of these cases, additional risk factors were present (immobilisation, APCresistance, obesity, and/or a history of a thromboembolic event). In the one case of pulmonary embolism, no additional risk factors were present.

Effects on haemostasis were initially evaluated in the large uncontrolled study by means of prothrombin time, antithrombin III and thrombocyte count. A slight decrease in antithrombin III activity (6%) and a slight increase in prothrombin time (thromboplastin time) occurred. The thrombocyte count remained unchanged. In the comparative study

versus Kliogest, antithrombin III activity was slightly increased (3% for Climodien 2/2, 6% for Climodien 2/3). An extensive investigation of coagulation/anticoagulation variables was performed in the study that investigated the clinical performance of Climodien 2/3 (JPH04095). In this study, prothrombin fragment 1+2 (F_{1+2}) was chosen as the main target parameter, which is considered a sensitive indicator for activation of coagulation activation. F_{1+2} was decreased in the Climodien 2/3 group as well as in the placebo group. The results gave no indication that coagulation activation increases during Climodien 2/3-medication. The marketing authorisation holder will start a post marketing study in which, among others, the incidence of venous thrombosis will be monitored. Concerning arterial thrombosis, two cases of myocardial infarction have been reported in the comparative study; one patient was treated with Climodien whereas the other used Kliogest. Both patients had risk factors for arterial disease.

Lipid metabolism
Treatment with Climodien 2/2 resulted in a slight reduction in total cholesterol and LDL levels. Regarding HDL cholesterol, changes occurred in different directions, varying from a decrease of 5% to an increase of 6%.

Additional claims

Urinary markers of vascular function
In an open comparative study, the primary focus was the measurement of potential surrogate markers of vascular function (primarily cGMP) in the overnight urine of postmenopausal women under estradiol valerate alone and under estradiol valerate + dienogest. An increase was noted in comparison with baseline values, which increase was not negatively influenced by the addition of dienogest.

Post marketing experience
Climodienwas not marketed in any country. However, ethinyl estradiol 50 µg + dienogest 2 mg (Sertostat) and ethinyl estradiol 50 µg + dienogest 2 mg (Valette) are registered in Germany for contraception.

Discussion on clinical trial results and evaluation criteria
The clinical program especially focussed on the safety of Climodien and endometrial efficacy of dienogest in the recommended dose. The decision on endometrial safety must be based on reliable data from a sufficient number of patients, treated for a sufficient time period. The CPMP Points to Consider on hormone replacement therapy, among others, considers the requirements necessary to evaluate adequately the risk for endometrial hyperplasia during hormone therapy, among others, in case of a new combination of estrogen/progestagen. The following requirements are recommended:

a) The number of patients should be large enough to provide a sufficiently precise estimate of the incidence of hyperplasia or more serious adverse endometrial outcomes, after one year of treatment;
b) The reported estimates of the incidence of these outcomes are approximately 0-1% for non-treated women and 1-2% for women treated with currently marketed HRT regimens. For a new HRT, a reasonable requirement on the precision is that the incidence should be determined to within 2%, i.e. that the upper limit of a one-sided 95% confidence interval should not exceed the point estimate by more than 2%. This requires approximately 300 patients treated for one year or approximately 150 patients treated for two years would give a similar precision.

In order to fulfil these requirements on endometrial safety, the already initiated pivotal comparative study versus Kliogest and Climodien 2/3, was extended with two year without interruption of treatment, in which all patients were treated with Climodien 2/2. The extension of this study was not yet completed, but the number of patients from whom an endometrial biopsy was available after one (290) and two year's treatment (191) was considered sufficient. No cases of endometrial hyperplasia were noted, but one case of adenocarcinoma was diagnosed, giving an incidence of 0.34. The corresponding upper limits of the 95% confidence interval over treatment periods of one and two years did not exceed the point estimate by more than 2%, indicating that the recommended requirement on the precision was met.

Another important marker of adequate progestagenic action is the observed bleeding pattern. In agreement with the Points to consider on HRT this parameter was evaluated for at least 12 months in a comparative design. The comparative study versus Kliogest indicated no clear differences in bleeding pattern between groups. As expected, the percentages of patients with amenorrhoe increased with time. At the end of the 12-month double-blind period, the percentage of women who had become amenorrhoeic was at least as high as noted for Kliogest (85% versus 81% for Kliogest). Bleeding data from the large uncontrolled study additionally supported the observed bleeding pattern.

The efficacy of estradiol valerate 2 mg in the treatment of postmenopausal symptoms is since long established. The presented extensive clinical data in this dossier have re-established the efficacy, which appeared not attenuated by the addition of dienogest 2 mg. Data from the pivotal comparative study indicated the efficacy of Climodien to be comparable with that of noted for Kliogest (estradiol 2 mg + norethisterone acetate 1 mg). These efficacy data on Climodien in this indication are additionally supported by the outcome of the supportive studies, in which treatment of climacteric symptoms was considered a secondary efficacy parameter. The efficacy of Climodien in this indication can be considered sufficiently proven by the clinical evidence presented.
The efficacy of Climodien 2/2 and Climodien 2/3 on postmenopausal sleep disorders versus estradiol valerate alone or placebo reported a non-significant decrease in nocturnal wakefulness time during treatment with Klimodien. These results did not justify the proposed claim of subjective improvement of sleeping disorders during treatment with Climodien under section 5.1 Pharmacodynamic properties.

The overall safety data indicated an adverse event pattern not clearly different from that known that known from other HRT's. Safety data coming from the comparative study versus Kliogest indicated the adverse event pattern of Climodien to be comparable with that noted for Kliogest.
In general, the number of patients included in the clinical studies that are part of the registration dossier is too low to give information on rare risks such as cancer, cardiovascular events and venous thrombosis. Comparative pharmacodynamic studies may indicate differences between products, but there are no generally accepted surrogate end points in the risk for cancer or venous thrombosis, the rare risks that are relevant in the treatment with a HRT. Although the information on these risks during use with Climodien is limited, the clinical dossier does not contain information that the increased risk for venous thrombosis and breast cancer is higher than for already approved hormone replacement therapies. Information on this point is considered adequately covered by the European harmonised SPC text on the increased risk for venous thrombosis and breast cancer in women using HRT. The company will start a post marketing study in which, among others, will focus on the incidence of venous thromboembolism.

The additional claim that effects of estrogens on vascular function were not negatively influenced by the addition of dienogest was not acceptable. The relevance of the measured increase of potential surrogate markers of vascular function (primarily cGMP) is unknown, because it is not clear how and in which way this increase might be an indicator that vascular function is improved. It was concluded that this was an experimental study (open-label, measurements not performed under standardised conditions, no comparison versus placebo), with debatable results. Further confirmation of the results and more clarity on the clinical relevance are needed before information on this subject can be accepted under 5.1 Pharmacodynamic properties.

Overall conclusion on quality, efficacy, safety and benefit/risk assessment

Quality

The chemical pharmaceutical documentation concerning the manufacturing, the quality of the raw materials and the finished product, and the stability of the product are sufficient with respect to the European regulatory rules.

Preclinical pharmacology and toxicology

The preclinical, pharmacological and toxicological properties of dienogest are in line with those of other synthetic progestagens.

Clinical efficacy and safety

Overall the clinical documentation for the hormone replacement therapy Climodien was considered appropriate. The clinical data met the requirements as recommended in the CPMP "Points to Consider on HRT on efficacy and safety in the situation of the combination of an estrogen with a new progestagen for protection of estrogen mediated unwanted stimulation of the endometrium".

Benefit/risk assessment

Overall, the clinical data led to the conclusion that the risk/benefit ratio for Climodien in the requested indication is positive. Efficacy and adverse event pattern are comparable with that of reference product Kliogest No conclusions can be drawn regarding the relative incidence of rare events, such as venous thrombosis and breast cancer. The rationale for the development of dienogest was to have a progestagen with strong anti-estrogenic and progestational effect and no androgenic effect. The question whether preclinically reported differences in receptor affinity of dienogest regarding the progesterone-, estrogen-, and androgen receptor may lead to any clinical advantage over approved progestagens cannot be answered on the basis of this registration file.
The SPC is adapted to the latest European opinions on the use of hormone replacement therapy. Although the European core SPC for HRT was still under discussion, consensus opinions were already included

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PUBLISHED CLINICAL STUDIES

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Mück A.O et al. Effect on biochemical vasoactive markers during postmenopausal hormone replacement therapy: estradiol versus estradiol/dienogest. Maturitas. 2001 May 30;38(3):305-13.