20 APR 2004

NEW HORMONE COMPOSITION AND ITS USE

The present invention relates to the field of therapeutic chemistry and more particularly to the field of pharmaceutical hormone technique.

More precisely, its objects are new pharmaceutical compositions formed of an estrogen-progestin association designed to correct estrogen deficiencies in women, regardless of their origin, and more particularly in menopausal women.

In particular its objective is an estrogen-progestin association characterised in that it consists of dose units containing a combination of a progestin and an estrogen, both compounds being present at the same time in each medicinal dose.

Specifically, its objects are new pharmaceutical compositions intended for hormone replacement therapy in menopause, which contain as active ingredient a progestational agent chosen from among nomegestrol and its esters and an estrogen agent chosen from among estradiol and its esters and the conjugated equine estrogens.

This association is intended for administration via the oral route, be it continuously or discontinuously.

As is known, over the course of less than a century the life expectancy of women has increased from 50 to 80 years, while the mean age at which the menopause begins has remained unchanged. Thus, women spend almost one-third of their life in a condition of estrogen deficiency, and this results in a higher risk of osteoporosis and cardiovascular disorders. Replacement therapy for the menopause has therefore become very widespread. It is administered either orally or, at least as regards its estrogen component, via the percutaneous route. Nevertheless, compliance seems better when the treatment is administered orally (ETTINGER et al., 1998).

Consecutive replacement therapy in the menopause cures the symptomatology of the climacteric. It prevents osteoporosis and the onset of cardiovascular disorders. It creates artificial cycles

which are followed by deprivational bleeding. This therapeutic scheme is particularly well suited to women whose menopause is recent, but it is not always well accepted in the long term, which partly explains the mediocre compliance with the treatment (DRAPIER FAURE E., Gynecology, 1992, 43: 271-280).

To overcome this drawback combined associations have been developed in which the two components are taken simultaneously, whether continuously or discontinuously, the effect of the progestin being to permanently oppose the proliferative action of the estrogen upon the endometrium, so inducing an atrophy of the endometrium and consequently preventing deprivation bleeding (HARGROVE J.T., MAXSON W.S., WENTZ A.C., BURNETT L.S., Obstet. Gynecol., 1989, 73: 606-612). In fact, under these conditions the endometrial atrophy is pronounced (WOLFE and PLUNKETT, 1994; PIEGSA et al., 1997; AFFINITO et al., 1998), there is no endometrial hyperplasia (STADBERG et al., 1996) and the frequency of bleeding is low and decreases with time (PIESGA et al., 1997; CARRANZA-LIRA, 1998; ETTINGER et al., 1998). With this type of treatment, compliance is generally good (EIKEN and KULTHOFF, 1995; DOREN et al., 1996), and certainly better than with consecutive treatment (EIKEN et al., 1996). The quality of life too seems improved (ULRICH et al., 1997). It is also known that this type of treatment protects the bone mass (EIKEN et al., 1996; EIKEN et al., 1997; HART et al., 1998; RECKER et al., 1999).

This "no-periods" scheme is particularly well suited for women whose menopause occurred already some time ago. Consecutive associations can be prescribed subsequently in order to improve long-term compliance with hormone replacement therapy in the menopause.

During consecutive treatments the progestin dose chosen is that which, in the long term, leads to at least 1% of endometrial hyperplasia when the progestin is administered discontinuously for more than 10 days per cycle in menopausal women undergoing estrogen replacement therapy (WHITEHEAD et al., J. Reprod. Med., 1982, 27: 539-548; PATERSON et al., Br. Med. J., 1980, 22 March: 822-824).

The progestin dose to be used in a combined replacement therapy is generally lower than that normally prescribed in consecutive schemes. Examples are micronised progesterone, dydrogesterone (FOX H., BAAK J., VAN DE WEIJER P., AL-AZZAWI E., PATERSON M.,

JOHNSON A., MICHELL G., BARLOW D., FRANCIS R., 7th International Congress on the Menopause, Stockholm, 20-24 June 1993, abstr. 119) and medroxyprogesterone acetate (BOCANERA R., BEN J., COFONE M., GUINLE I., MAILAND D., SOSA M., POUDES G., ROBERTI A., BISO T., EZPELETA D., PUCHE R., TOZZINI R., 7th International Congress on the Menopause, Stockholm, 20-24 June 1993, abstr. 40), which have been used respectively at doses of 100, 10 and 5 mg/day with encouraging results at the clinical and endometrial level.

Combined treatment is most often used continuously i.e. without interruption. Some, however, prefer to use it intermittently, for example on 25 days each month (BIRKAUSER M., et al.; Hormone substitution: a well defined indication and individual treatment schemes are decisive for the success of the therapy, Med. & Hyg., 1995, 53: 1770-1773). The purpose of interrupting the treatment is to remove the inhibition by the progestin of the synthesis of estradiol and progesterone receptors and so to avoid reducing the receptivity of the hormone-dependent tissues.

The progestin used according to the present invention is nomegestrol or one of its esters, notably nomegestrol acetate. Nomegestrol acetate is a powerful progestin which is active via the oral route and has an original pharmacological profile:

- in contrast to the derivatives of 19-nortestosterone, nomegestrol acetate shows no residual androgenic and estrogenic action;
- in common with the derivatives of 17-alpha-hydroxyprogesterone it has a pure pharmacological profile, but in contrast to them it has a powerful antigonadotropic action.

It belongs to the category of qualified hybrid progestins (OETTEL et al., 1999), which have no harmful metabolic effects because of the absence of a 17-alpha-ethinyl function, and which combine the advantages of the progesterone derivatives with those of the most modern among the 19-nortestosterone derivatives.

Its use in consecutive administration during the menopause at a dose of 5 mg/day for 12 days per cycle, in association with various types of estrogens, makes it possible to prevent endometrial hyperplasia as has been shown by a multicentric trial in 150 women over 1 year (THOMAS J.L., BERNARD A.M., DENIS C., 7th International Congress on the Menopause, Stockholm, 20-24 June 1993, abstr. 372).

The absence of hyperplasia was confirmed in a study in which nomegestrol acetate was administered at the same dose for 14 days per cycle to women being treated with percutaneous estradiol (BERNARD A.M. et al., Comparative evaluation of two percutaneous estradiol gels in combination with nomegestrol acetate in hormone replacement therapy. XIV World Congress of Gynecology and Obstetrics, FIGO, Montreal, 24-30 September 1994). This utilisation, which is covered by French Patent No. 2.737.411 in the name of the Applicant Company, claims a dose range from 1.5 to 6 mg and preferably from 2.5 to 5 mg.

The estrogen used is estradiol, free or esterified, and in particular estradiol valerate, or the conjugated equine estrogens, presented in a formulation that is active via the oral route. It has been shown that an estradiol dose of between 1 and 2 mg/day is enough to combat the estrogen deficiency in menopausal women.

The nomegestrol acetate and free or esterified estradiol, or the conjugated equine estrogens are administered in one of the forms that enable oral administration: gelatine capsules, capsules, pills, powder sachets, tablets, coated tablets, sweetened tablets, etc.

The present invention is characterised by the fact that it is a new estrogen-progestin association which is active via the oral route, and is administered in combination. A further object of this invention is the use of compositions according to the invention to correct estrogen deficiencies and to prevent osteoporosis and cardiovascular disorders in menopausal women.

The present invention is also defined by:

a) **The fact that the estrogen-progestin association concerned is different from those described before now for the same type of indications.**

Certain patents claim the continuous use of estrogen-progestin combinations for replacement therapy in menopause. Examples are the patents US 5108995 or EP 309263. It is evident, however, that these patents claim multisequential treatments with dose changes of the active

ingredients. This is also true of the patents filed in the USA (US 4820831 A) and in Europe (EP 136 011) in the name of PLUNKETT. Those patents claim the use of numerous estrogens and numerous progestins in menopause replacement therapy. It seems, however, that the said claims do not cover the use of all progestins, on the one hand for scientific reasons and on the other hand for scientific and legal reasons related to the wording of the claims of the two said patents:

1) The use of numerous progestins is based on equivalences with one of them, in the event levonorgestrel. This approach seems unacceptable because different progestins have very different pharmacological profiles and the doses to be used cannot be deduced from a simple and unique equivalence system, as becomes clear from the active dose ranges proposed for different progestins in 3 different patents (Table 1).

It can be seen that the lower limit for the various progestins varies in a ratio of 2.4 to 50 while the maximum dose varies in a ratio of 1 to 50. Thus, for indications of the same type, the dose range varies very considerably from one patent to the next and this shows that the system of equivalence does not lend credibility to the relations which could be established between progestins.

2) Apart from the above, it would be reasonable to think that the doses claimed should be based on data from clinical pharmacology and/or clinical data previously published and commonly accepted. Now, if the doses defined as in the PLUNKETT patents are considered, it is easy to see that in most cases the active doses published already a long time ago, i.e. before the said patents were filed (NEUMANN, 1977) or more recently (KUHL, 1996), are very coherent but only rarely lie within the dose ranges claimed in the patents in the name of PLUNKETT (Table 2).

This finding is also valid if, instead of the active doses as above, account is taken of the active dose ratios given by taking norgestrel as reference (= 1) (Table 3).

Table No. 1 Doses (µg/day) of the various progestins claimed according to the patents

PROGESTIN	PATENT	DOSE (µg/day)	
		Minimum	Maximum
Levonorgestrel	WO 95/17194	60	125
Levonorgestrel	EP 025607 A1	25	100
Levonorgestrel	PLUNKETT	25	75
Gestodene	WO 95/17194	50	75
Gestodene	EP 025607 A1	10	70
Desogestrel	WO 95/17194	60	150
Desogestrel	EP 025607 A1	25	100
3-ketodesogestrel	WO 95/17194	60	150
3-ketodesogestrel	EP 025607 A1	25	100
Norethisterone	WP 95/17194	350	750
Norethisterone	EP 025607 A1	85	350
Norethisterone	PLUNKETT	150	1 000
Norethisterone acetate	PLUNKETT	100	1 000
Norgestimate	WO 95/17194	200	300
Norgestrel	PLUNKETT	50	150
Ethynodiol diacetate	PLUNKETT	100	1 000
Dihydrogesterone	PLUNKETT	5 000	30 000
MPA	PLUNKETT	1 000	15 000
Norethynodrel	PLUNKETT	200	5 000
Allylestrenol	PLUNKETT	1 000	10 000
Lynoestrenol	PLUNKETT	100	2 000
Quingestanol acetate	PLUNKETT	50	1 000
Medrogestone	PLUNKETT	1 000	10 000
Norgestrienone	PLUNKETT	20	200
Dimethisterone	PLUNKETT	500	15 000
Ethisterone	PLUNKETT	1 000	25 000
Cyproterone acetate	PLUNKETT	100	10 000
Cyproterone acetate	WO 95/17194	100	200

Table No. 2
Doses of each progestin according to the various bibliographical references

	US Pat. 4826831		NEUMANN PUBLICATION				KUHL	
	Min.	Max.	Endometrium (1)	Menstruation (2)	Ovulation (3)	Contraception (4)	Endometrium (1)	Ovulation (3)
Levonorgestrel	25	75					**400**	60
Norgestrel	50	150	**1200**	**2000**	100	**250**		
Norethisterone	150	1000	**12500**	**5000**	800	1000	**10000**	400
Norethisterone acetate	100	1000	**4500**		800	1000		
Ethynodiol diacetate	100	1000						
Dydrogesterone	5000	30000						
MPA	1000	15000	5500	**25000**		5000		
Norethynodrel	200	5000	**10000**	**7500**	6000	2500		
Allylestrenol	1000	10000	1750					
Lynoestrenol	100	2000	**5000**			**2500**		
Quingestanol acetate	50	1000						
Medrogestone	1000	10000						
Norgestrienone	20	200						
Dimethisterone	500	15000						
Ethisterone	1000	25000						
CIP acetate	100	10000	1000		1000	2000	2000	1000

The cases appearing **in bold** above correspond to active doses outside the dose ranges claimed in the "PLUNKETT" patents. The doses (**µg/day**) are those necessary to induce transformation of the endometrium (1), to produce an adequate delay in the onset of periods (2), to inhibit ovulation (3), or to have a contraceptive effect (4).

20 APR 2004

Table No. 3: Dose ratios of each progestin according to the various bibliographical references
The reference progestin is norgestrel (= 1)

	US Pat. 4826831		NEUMANN			
	Ratios		Ratios			
	Min.	Max.	Endometrium (1)	Ovulation (3)	Menstruation (2)	Contraception (4)
Levonorgestrel	0.5	0.5				
Norgestrel	1.0	1.0	1.0	1.0	1.0	1.0
Norethisterone	3.0	6.7	***10.4***	***8.0***	***2.5***	4.0
Norethisterone acetate	2.0	6.7	3.8	***8.0***		4.0
Ethynodiol diacetate	2.0	6.7				
Dydrogesterone	100.0	200.0				
MPA	20.0	100.0	***4.6***		***12.5***	20.0
Norethynodrel	4.0	33.3	8.3	***60.0***	***3.8***	10.0
Allylestrenol	20.0	66.7	***1.5***			
Lynoestrenol	2.0	13.3	4.2			10.0
Quingestanol acetate	1.0	6.7				
Medrogestone	20.0	66.7				
Norgestrienone	0.4	1.3				
Dimethisterone	10.0	100.0				
Ethisterone	20.0	166.7				
CIP acetate	2.0	66.7	***0.8***	10.0		8.0

The cases appearing ***in bold and Italics*** correspond to active doses outside the ratio ranges claimed in the US and EP patents cited in the name of PLUNKETT. For the meanings of (1), (2), (3) and (4), see Table 2.

20 APR 2004

Reasoning related to the claims

1) In the US patent cited above, Claims 1 and 2 concern continuous treatments; the only progestins claimed are di-norgestrel and levonorgestrel. The subsequent claims concern discontinuous multisequential treatment, i.e. a therapeutic scheme different from that proposed in the present patent application. For this latter type of therapeutic regime the number of progestins claimed is larger but the list thereof is precise and limited, as emerges from the Markush-type presentation of the said claims, and it does not include nomegestrol and its esters.

2) The European patent only claims the continuous combined treatment; the estrogens and progestins claimed are listed in tables present in the body of the text and summarised in the claims. There too, nomegestrol and its esters do not feature in the lists of progestins that can be used. Now, nomegestrol acetate is characterised by a powerful progestational action, an absence of residual androgenic and estrogenic effects, and a powerful anti-estrogenic action which is manifested at the level of the endometrium by marked anti-mitotic activity and, consequently, a pronounced atrophying effect. Accordingly, it cannot be likened to the other progestins and to think in terms of a dose correspondence relative to another progestin taken as reference cannot but be erroneous. Moreover, nomegestrol acetate is characterised by excellent tolerance; it has no effect on the lipids profile, the tolerance to glucides, the arterial pressure and the coagulation factors, even when used at doses higher than those described in the present patent application and in prolonged treatments (BASDEVANT et al., 1997). This aspect is very important because all therapists in common strive to use the treatment with least possible toxicity involving the lowest possible doses. In this respect, nomegestrol acetate differs from many derivatives of 19-nortestosterone cited in the PLUNKETT patents, which are progestins characterised by androgenic and estrogenic effects which can have consequences at the level of the endometrium and which also have harmful metabolic effects.

For the same reasons as those mentioned above, none of the numerous publications that deal with the continuous combined treatment of the menopause can have a bearing on the present invention because none of these publications deals with an association of nomegestrol acetate with an estrogen. This for example applies to associations of estradiol and norethisterone

acetate (STADBERG et al., 1996; DOREN and SCHNEIDER, 1996; DOREN et al., 1997; EIKEN et al., 1997; PIEGSA et al., 1997; HART et al., 1998), estradiol and medrogestone (AFFINITO et al., 1998), estradiol and norgestrel (WOLFE and PLUNKETT, 1994), estradiol valerianate and chlormadinone acetate (RAUCH and TAUBERT, 1993), and conjugated equine estrogens with medroxyprogesterone acetate (REUBINOFF et al., 1995; WOLFE and HUFF, 1995; MIZUNUMA et al., 1997) or medrogestone (RECKER et al., 1999).

b) The fact that this estrogen-progestin association is different from the association previously patented by the Applicant Company.

In effect, French Patent No. 2.754.179 in the name of the Applicant Company claimed an association of estradiol and nomegestrol acetate for the combined replacement therapy of the menopause. The dose range claimed on the basis of previous experience with nomegestrol acetate in consecutive therapy was from 1.5 to 3.75 mg, preferably 2.5 mg. Now, clinical trials on a broader scale have shown that in an unexpected way, very much lower doses of nomegestrol acetate can induce endometrial atrophy with very good control of bleeding. This observation is important because it allows the nomegestrol acetate doses to be reduced still further, so that it can be used with still greater safety.

c) Appropriate production method for the pharmaceutical forms

The invention concerns a production method with which the two active ingredients can be combined in one and the same pharmaceutical form.

The compositions according to the invention, based on nomegestrol acetate and free or esterified estradiol or conjugated equine estrogens, are administered either continuously or intermittently (from 21 to 28 days per month).

According to a particular embodiment of the invention, the compositions contain a quantity of nomegestrol acetate ranging from 0.3 to 1.5 mg and a quantity of free or esterified estradiol or conjugated equine estrogens ranging from 0.3 to 3 mg. Preferably, the optimum formulations contain 0.625 to 1.25 mg of nomegestrol acetate associated with 0.5 to 1.5 mg of free

estradiol or 1.5 to 2 mg of estradiol ester or 0.312 to 0.625 mg of conjugated equine estrogens, in each daily dose.

This mode of combined administration is indicated in menopausal women, whether the menopause is natural or the result of surgery; the estrogen-progestin combination is intended to compensate the functional disturbances induced by the menopausal estrogen deficiency, while maintaining endometrial atrophy and avoiding the appearance of deprivation bleeding in most of the women.

A further objective of the present invention is a process for obtaining new pharmaceutical compositions, which consists in mixing the active ingredients: nomegestrol acetate and free or esterified estradiol or conjugated equine estrogens, with one or more inert, non-toxic and pharmaceutically acceptable excipients or vehicles.

Among the excipients may be mentioned binding and dissolution-promoting agents, compaction agents, disintegration agents and slip-promoting agents.

The said mixture is compacted directly or in several stages to form tablets which can be protected on the surface, if desired, with a film, a coating, or by being made into sweets. The production of tablets by direct compaction makes possible the maximum reduction of the proportion of dilution agents, binding agents, disintegration agents and slip-promoting agents.

Gelatine capsules can be produced by mixing the active ingredients with an inert diluent and with a slip-promoting agent.

The tablets contain, in particular, agents which dilute the mass such as lactose, sorbitol for direct compaction, as marketed under the name NEOSORB 60, Palatinite which is the registered trade name designating an equimolar mixture of isomer of [D]glucopyranosido-1,6-mannitol and [D]glucopyranosido-1,6-glucitol crystallised with two water molecules, mannitol, sorbitol, or the lactose/PVP mixture marketed under the name Ludipress.

The compaction binding agents are generally microcrystalline celluloses such as those marketed under the name AVICEL PH 101 or AVICEL PH 102. Polyvinylpyrrolidone also plays an important part by facilitating the agglomeration of the powders and the compressibility of the mass. The polyvinylpyrrolidones used for this purpose have molecular weights between 10 000 and 30 000, such as Povidone, or Kollidon graded from 12 to 30.

The mixture also contains slip-promoting or anti-electrostatic agents which prevent the powder from agglomerating in the feed hoppers. In this connection the colloidal silicas marketed under the name AEROSIL, 100 or AEROSIL 200 may be mentioned.

The mixture also contains disintegration agents which make for disintegration or crumbling in accordance with pharmaceutical standards. As useful disintegration agents may be mentioned the cross-linked vinylpyrrolidone polymers such as those marketed under the names Polyplasdone or Polyclar AT, carboxymethyl starches such as those marketed under the names Amijel or Explotab, or cross-linked carboxymethyl celluloses such as the compound sold under the name AC-DI-SOL.

In addition, the preparation contains lubricant agents which facilitate compaction and the ejection of the tablet from the tableting machines. As lubricants may be mentioned glycerol palmitostearate as sold under the name Precirol, magnesium stearate, stearic acid or talc.

After compaction the tablets can be coated to improve their storage properties or to facilitate swallowing.

The coating agents are cellulosic, such as cellulose phthalate (Sepifilm, Pharmacoat), or polyvinyl of the OPADRY PVA or Sepifilm ECL type, or saccharosic such as sweet-making sugar of the Sepisperse DR, AS, AP or K types (coloured).

The tablets, whether coated or not, can in addition be coloured at the surface or throughout, with mineral, vegetable or synthetic dyes (for example lacquer with quinoline-yellow, or E 104 or iron oxides).

The proportions of the various constituents vary according to the nature of the tablet to be made.

The content of active ingredients can range from 0.3 to 1.5 mg for the nomegestrol acetate and from 0.3 to 3 mg for the free or esterified estradiol or for the conjugated equine estrogens. The dilution agents range from 20 to 75% of the total mass, the slip-promoters from 0.1 to 2% of the total mass, the compaction binding agents range from 2 to 20%, the polyvinylpyrrolidone from 0.5 to 15%, the disintegration agents range from 2 to 5.5% for cross-linked polyvinylpyrrolidone or carboxymethyl starch, and from 2.0 to 3.0% for croscarmellose.

The quantities of lubrication agents vary from 0.1 to 3.0%, depending on the type of agent.

The compositions according to the invention are intended to be administered once per day. However, depending on the therapeutic needs, the administration may be divided (twice daily) or, on the contrary repeated (two tablets per day).

The following examples illustrate the invention without limiting it in any way.

EXAMPLE 1: Examples of formulations

The association of nomegestrol acetate and estradiol is presented in the form of plain or filmed tablets.

The mixture of ingredients can either be compacted directly, or a preliminary estradiol mixture can be made into which the nomegestrol acetate and the other excipients are then incorporated in dry form. The preliminary estradiol mixture is made by dissolving the estradiol in an alcoholic solution of microcrystalline cellulose, PVP and lactose, drying it, and then grinding and calibrating it. This process is advantageous because tablets made from a preliminary estradiol mix have an estradiol dissolution profile which is appreciably better compared with tablets made by direct compaction.

The final mixture can contain from 1.5 to 5% of estradiol in povidone (5 to 25%), microcrystalline cellulose (5 to 15%) and lactose (enough to make up to 100%). It can be advantageous to introduce an anti-oxidant agent such as alpha-tocopherol or ascorbic acid during the preparation of the preliminary mix.

As an example, the following preliminary mix can be mentioned:

FORMULATIONS	in mg/one tablet	in %
Estradiol	1.50	1.82
PVP K25	13.50	16.36
Lactose 8195	60.00	72.73
Microcrystalline cellulose	7.50	9.09
TOTAL DRY MIX	**82.50**	**100.00**

This preliminary mix is introduced into the final mixture to obtain a tablet by direct compaction.

The finished tablets, uncoated, generally weigh 60 to 200 mg and have the following overall formulation:

FORMULATIONS OF THE UNCOATED TABLETS

Composition

		in mg per tablet
-	Estradiol (pre-mix, quantity sufficient for)	**0.3 to 3.0**
-	Nomegestrol acetate	**0.300 to 1.500**
-	Colloidal silica	0.400 to 2.000
-	Crospovidone	2.500 to 4.000
-	Lactose	60.000 to 80.000
-	Cellulose	10.000 to 25.000
-	Stearic acid	0.900 to 3.000
-	Talc	0.450 to 1.500

As examples, tablets can be mentioned which weigh 185 mg and have the following formulas:

Example of the formulation (UF = unitary formulation) of 185 mg tablets

FORMULATION	**UF mg per 1 tablet of 185 mg**	**UF %**
Estradiol	1.500	0.811
Nomegestrol acetate	**0.625**	0.338
Lactose	131.790	71.238
Cellulose (Avicel PH 101)	27.810	15.032
Povidone (K25)	13.500	7.297
Precirol (AT05)	2.780	1.503
Colloidal silica (Aerosil 200)	1.000	0.540
Crospovidone (Polyplasdone XL)	6.000	3.243
TOTAL	**185.00**	100.000

Example of the formulation (UF = unitary formulation) of 185 mg tablets

FORMULATION	UF mg per 1 tablet of 185 mg	UF %
Estradiol	0.500	0.270
Nomegestrol acetate	**0.625**	0.339
Lactose	136.787	73.934
Cellulose (Avicel PH 101)	32.813	17.736
Povidone (K25)	4.500	2.432
Precirol (AT05)	2.775	1.500
Colloidal silica (Aerosil 200)	1.000	0.540
Crospovidone (Polyplasdone XL)	6.000	3.243
TOTAL	**185.00**	**100.000**

Example of the formulation (UF = unitary formulation) of 120 mg tablets

FORMULATION	UF mg per 1 tablet of 120 mg	UF %
Estradiol	1.500	1.250
Nomegestrol acetate	**1.250**	1.042
Lactose	84.000	70.000
Cellulose (Avicel PH 101)	11.250	9.375
Povidone (K25)	13.500	11.250
Colloidal silica (Aerosil 200)	1.000	0.833
Crospovidone (Polyplasdone XL)	3.000	2.500
Magnesium stearate	1.000	0.833
Talc	1.000	0.833
Stearic acid AC/50VG	2.500	2.083
TOTAL	**120.00**	**100.000**

Example of the formulation (UF = unitary formulation) of 120 mg tablets

FORMULATION	UF mg per 1 tablet of 120 mg	UF %
Estradiol	0.500	0.417
Nomegestrol acetate	**0.625**	**0.521**
Lactose	89.000	74.167
Cellulose (Avicel PH 101)	16.875	14.062
Povidone (K25)	4.500	3.750
Colloidal silica (Aerosil 200)	1.000	0.833
Crospovidone (Polyplasdone XL)	3.000	2.500
Magnesium stearate (vegetable)	1.000	0.833
Talc	1.000	0.833
Stearic acid AC/50VG (vegetable)	2.500	2.083
TOTAL	**120.00**	**100.000**

Example of the formulation (UF = unitary formulation) of 80 mg tablets

FORMULATION	UF mg per 1 tablet of 80 mg	UF %
Estradiol	0.500	0.625
Nomegestrol acetate	**0.625**	0.781
Kollidon 25	4.500	5.625
Lactose M	59.735	74.669
Cellulose (Avicel PH 101)	12.000	15.000
Crospovidone (Polyplasdone XL)	0.800	1.000
Talc	0.700	0.550
Colloidal silica (Aerosil 200)	0.440	0.550
Magnesium stearate (vegetable)	0.700	0.875
TOTAL	**80.000**	**100.000**

Example of the formulation (UF = unitary formulation) of 80 mg tablets

FORMULATION	UF mg per 1 tablet of 80 mg	UF %
Estradiol	1.000	1.250
Nomegestrol acetate	1.250	1.563
Kollidon 25	9.000	11.250
Lactose M	54.110	67.637
Cellulose (Avicel PH 101)	12.000	15.000
Crospovidone (Polyplasdone XL)	0.800	1.000
Talc	0.700	0.875
Colloidal silica (Aerosil 200)	0.440	0.550
Magnesium stearate (vegetable)	0.700	0.875
TOTAL	**80.000**	**100.000**

These tablets may be coated, for example with:

- filming agents based on polyvinyl alcohol of the type OPADRY PVA "moisture barrier" (polyvinyl alcohol, titanium dioxide, purified talc, lecithin, xanthane gum, pigments, lacquers),

or

- filming agents based on cellulose of the type SEPIFILM L.P. ([H.P.M.C. (hydroxypropylmethylcellulose)], microcrystalline cellulose, stearic acid, pigments, lacquers).

EXAMPLE II: Dissociation of the antimitotic and differentiating effects of nomegestrol acetate on endometrial cells

Menopausal women, whether naturally or as the result of surgery, were subjected to a sequential estrogen-progestin therapy. From Day 1 to Day 12 they received 30 µg of ethinyl estradiol and then, from Day 13 to Day 22, the same dose of ethinyl estradiol associated with different doses of nomegestrol acetate or chlormadinone acetate. The doses were as follows:

Nomegestrol acetate (mg):	0.1	0.25	0.5	1		2.5	5	and 10
Chlormadinone acetate (mg):	0.1		0.5	1	2		5	and 10

The number of women was between 2 and 11, depending on the group. There was then a therapeutic pause of 7 days followed by a second treatment cycle.

The parameters taken into account were as follows:

- the interval before periods commenced after the therapy had been interrupted, following the first and second treatment cycles;

- the histological appearance of the endometrium recovered in a biopsy carried out between Day 17 and Day 20 of the second cycle.

The results showed that:

- The interval before periods appeared is a function of the dose and is similar for both products. The dose required for no periods to appear before the end of the therapy is between 0.2 and 0.3 mg/day for both products (Table 1).

- The transformation of the endometrium into a secretory endometrium is total with both products from 1 mg/day upwards, but decreases at the highest doses (10 mg/day).

- The proliferation activity, expressed as the number of mitoses in the glandular cells, seems more strongly inhibited by nomegestrol acetate than by chlormadinone acetate. Mitosis no longer takes place in women treated with a dose equal to or higher than 0.5 mg/day of nomegestrol acetate, while mitosis is still evident with a daily dose of 1 mg/day of chlormadinone acetate (Table 2).

It can therefore be concluded that at the endometrial level, nomegestrol acetate and chlormadinone acetate are not comparable: the secretory transformation activity is comparable but nomegestrol acetate is characterised by a very marked antimitotic and antiproliferative action.

Table 1: Interval before the appearance of periods (days) after the therapy is discontinued

Progestin	Dose (mg/day)							
	0.1	0.25	0.5	1.0	2.0	2.5	5	10
Nomegestrol acetate	- 0.5 ± 1.5	- 0.5 ± 0.5	1.5 ± 0.5	2.7 ± 0.2		3.2 ± 0.2	4.3 ± 0.4	3.8 ± 0.8
Chlormadinone acetate	- 2.3 ± 0.5		2.0 ± 0.6	3.8 ± 0.3	3.8 ± 0.3		5.5 ± 1.5	5.5 ± 0.5

Table 2: Evaluation of the number of mitoses (% of section in which mitoses were present)

		Dose (mg/day)							
		0.1	0.25	0.5	1	2	2.5	5	10
Glands	Nomegestrol acetate	50	50	0	0	0	0	0	30
	Chlormadinone acetate	90			50	0		0	0

EXAMPLE III:

A trial was carried out to study the effects on the endometrium of the continuous combined association of an oral estradiol dose equivalent to 1.5 mg and various doses of nomegestrol acetate.

This consisted in the treatment for 6 consecutive months of 179 women who had been menopausal for at lest 3 years, with 1.5 mg per day of estradiol combined continuously with 4 different doses of nomegestrol acetate: 5 mg/day (n = 47); 2.5 mg/day (n = 42); 1.25 mg/day (n = 43) and 0.625 mg/day (n = 47).

The impact of these four associations on the endometrium was evaluated by recording the characteristics of genital bleeding, measuring the thickness of the endometrium by endovaginal echography before and at the end of the therapy, and by carrying out a biopsy of the endometrium before and at the end of the therapy.

The percentages of women who showed no genital bleeding at all throughout the therapy were respectively 42.5 - 58.1 - 52.4 and 68.1%, with the doses of 0.625 - 1.25 - 2.5 and 5 mg of nomegestrol acetate per day. The percentages observed are not statistically different between the groups, but the relation between the dose and the incidence of bleeding is significant.

The tables attached indicate, for each nomegestrol acetate dose, the results of the echographic examination and biopsy of the endometrium carried out at the end of the 6 months of treatment.

At the end of the therapy, the mean thickness of the endometrium is not different between the groups. The increase of the endometrial thickness under therapy is 0.39 mm on average with the smallest nomegestrol acetate dose. This thickening increases slightly as a function of dose, becoming 1.56 mm in the group of women who received 5 mg/day of the progestin, but the relation between the variation of thickness and the dose variation does not reach the threshold of statistical significance.

20 APR 2004

The biopsies of the endometrium examined at the end of the trial showed no proliferative or hyperplasic appearance of the uterine mucosa. The highest percentage of secretory endometria was observed in the women who had received the highest progestin dose; it decreased progressively and in a statistically significant way with the dose. In contrast, the highest percentage of atrophic endometria was found at the lowest progestin dose and this decreased as the dose increased.

These results are unexpected in the sense that they show that low doses of nomegestrol acetate administered in continuous combination with an estrogen are capable of preventing the growth of the uterine mucosa and keeping it in an atrophic condition, whereas, in contrast to higher doses, they are insufficient to induce a secretory transformation of the endometrium.

Thus, this trial reveals a surprising decoupling of the anti-estrogenic effect of nomegestrol acetate from its progestational effect, when it is administered in continuous combination with estrogens.

The anti-estrogenic effect is preponderant since it is detectable when the progestin, administered continuously with an estrogen, is given at low doses. These doses are insufficient to bring about secretory transformations of the uterine mucosa. At higher doses and with the same therapeutic scheme, the secretory effect predominates, though without allowing excessive proliferation of the endometrium.

Table I - **Endometrial thickness after 6 months of continuous treatment with several combined associations based on estradiol (2 mg of estradiol valerate) and nomegestrol acetate (NOMAC) at various doses**

Doses of NOMAC (mg/day)	0.625 (n = 35)	1.25 (n = 33)	2.5 (n = 34)	5 (n = 41)
Mean thickness at the end of the treatment (mm)	3.18 (1.65)	4.05 (3.75)	3.93 (2.10)	3.83 (2.72)
Mean thickness increase under the treatment (mm)	0.39 (1.67)	1.12 (3.67)	1.36 (1.54)	1.57 (2.39)

( ) = standard deviation

20 APR 2004

Table 2 - **Histological appearance of the endometrium after 6 month of continuous treatment with several combined associations containing estradiol (2 mg of estradiol valerate) and nomegestrol acetate (NOMAC) at various doses**

Doses of NOMAC (mg/day)	0.625 (n = 32)	1.25 (n = 33)	2.5 (n = 34)	5 (n = 40)
Absence of endometrium	5 (15.6)	10 (30.3)	3 (8.8)	3 (7.5)
Atrophic endometrium	19 (59.4)	10 (30.3)	8 (23.5)	3 (7.5)
Secretory endometrium	8 (25.0)	12 (36.4)	22 (64.7)	34 (85.0)
Polyps	0	1 (3.0)	1 (2.9)	0

( ) = percentage

In no case was the endometrium proliferative or hyperplasic.

20 APR 2004

CLAIMS

1. Use of an oral composition containing from 0.3 to 3 mg of an estrogen component, from 0.3 to 1.25 mg of a progestative component selected from nomegestrol and esters thereof, and one or more pharmaceutically acceptable excipient(s),
in the preparation of a medicament intended to correct estrogen deficiencies in women, in particular in menopausal women.

2. Use of an oral composition containing from 0.3 to 3 mg of an estrogen component, from 0.3 to 1.25 mg of a progestative component selected from nomegestrol and esters thereof, and one or more pharmaceutically acceptable excipient(s),
in the preparation of a medicament intended to prevent osteoporosis in menopausal women.

3. Use according to claim 1 or 2, wherein the estrogen component is selected from free or esterified 17β-estradiol and conjugated equine estrogens.

4. Use according to one of claims 1 to 3, wherein the estrogen component is free 17β-estradiol.

5. Use according to one of claims 1 to 3, wherein the estrogen component is an ester of 17β-estradiol.

6 Use according to claim 5, wherein the ester of 17β-estradiol is estradiol valerate.

7. Use according to one of claims 1 to 3, wherein the estrogen component consists of conjugated equine estrogens.

8. Use according to claim 4, wherein the composition contains from 0.5 to 1.5 mg of free 17β–estradiol.

9. Use according to claim 5 or 6, wherein the composition contains from 1.5 to 2 mg of ester of 17β-estradiol.

10. Use according to claim 7, wherein the composition contains from 0.312 to 0.625 mg of conjugated equine estrogens.

11. Use according to one of claims 1 to 10, wherein the progestative component is nomegestrol acetate.

12. Use according to claim 11, wherein the composition contains from 0.625 to 1.25 mg of nomegestrol acetate.

13. Use according to one of claims 1 to 12, wherein the medicament is intended to be administered continuously.

14. Use according to one of claims 1 to 12, wherein the medicament is intended to be administered from 21 to 28 days per month.