



\*159159\*

## **A NEW HORMONAL COMPOSITION AND ITS USE**



\*G00002\*

5 The present invention relates to the field of therapeutic chemistry and more particularly to the field of pharmaceuticals.

More precisely, it relates to new pharmaceutical compositions formed from an estrogen-progestogen combination with the aim of correcting estrogen deficiencies in women, of all origins, and more especially in menopausal women.

10 It relates in particular to an estrogen-progestogen combination, characterized in that it consists of dosage units containing a combination of a progestogen and an estrogen the two components of which are present simultaneously in each unit dose.

It relates specifically to novel pharmaceutical compositions intended for hormone replacement therapy for menopausal women, containing as active ingredients a  
15 progestative agent selected from nomegestrol and its esters and an estrogenic agent selected from estradiol and its esters and the conjugated estrogens.

This combination is intended to be administered orally, continuously or intermittently.

20 As is well known, the life expectancy of women has increased from 50 to 80 years in less than a century, whereas the average age of onset of the menopause has not changed. Thus, women spend nearly a third of their life in a state of estrogen deficiency, giving rise to an increased risk of osteoporosis and cardiovascular diseases. Replacement therapy during the menopause has therefore become very common. It is  
25 administered either orally or, at least for its estrogen component, percutaneously. However, compliance seems better in the case of oral administration (ETTINGER et al., 1998).

Sequential replacement therapy in menopausal women cures menopausal symptoms. It  
30 prevents osteoporosis and the onset of cardiovascular diseases. It creates artificial cycles that are followed by withdrawal bleeding. This treatment regimen is especially

suitable for women whose menopause is recent but it is not always well accepted in the long term, which partly explains the poor adherence to the treatment (DRAPIER FAURE E., *Gynécologie*, 1992, 43: 271-280).

5 To overcome this drawback, combinations have been developed in which the two components are taken simultaneously, either continuously or intermittently, the progestogen having the effect of permanently countering the proliferative action of estrogen on the endometrium, by causing atrophy of the endometrium and, in consequence, the absence of withdrawal bleeding (HARGROVE J.T., MAXSON W.S.,  
10 WENTZ A.C., BURNETT L.S., *Obstet. Gynecol.*, 1989, 73: 606-612). In fact, in these conditions, there is considerable endometrial atrophy (WOLFE and PLUNKETT, 1994; PIEGSA et al., 1997; AFFINITO et al., 1998), there is no endometrial hyperplasia (STADBERG et al., 1996) and bleed frequency is low and decreases with time (PIEGSA et al., 1997; CARRANZA-LIRA, 1998; ETTINGER et al., 1998). With this type of  
15 treatment, adherence is generally good (EIKEN and KULTHOFF, 1995; DOREN et al., 1996), and better than with sequential treatment (EIKEN et al., 1996). Quality of life also seems improved (ULRICH et al., 1997). It is also known that this type of treatment protects bone mass (EIKEN et al., 1996; EIKEN et al., 1997; HART et al., 1998; RECKER et al., 1999).

20 This regimen "without periods" is particularly suitable for women whose menopause is already of long standing. It can be prescribed to alternate with sequential combinations for improving the long-term adherence to hormone replacement therapy at the menopause.

25 In sequential treatments, the dose of progestogen selected is that which leads in the long term to less than 1% of endometrial hyperplasia when the progestogen is administered intermittently, more than 10 days per cycle, in menopausal women receiving estrogen replacement therapy (WHITEHEAD et al., *J. Reprod. Med.*, 1982,  
30 27: 539-548, PATERSON et al., *Br. Med. J.*, 1980, 22 March: 822-824).

The dose of progestogen to be used in combined replacement therapy is generally deduced from what is usually prescribed in sequential regimens.

Examples of this are micronized progesterone, didrogesterone (FOX H., BAAK J., VAN DE WEIJER P., AL-AZZAWI E., PATERSON M., JOHNSON A., MICHELL G.,  
 5 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 of the Menopause, Stockholm, 20-24 June 1993, Abstr. 40) which have been used at  
 10 respective doses of 100, 10 and 5 mg/day, with encouraging results in clinical terms and with respect to endometrial effects.

Most often, combined treatment is used continuously, i.e. without interruption. Some therapists, however, favour using it intermittently, for example 25 days per month (BIRKAUSER M. et al.: Hormone replacement: well-founded indication and individual  
 15 treatment regimens are decisive for successful treatment, Méd. et Hyg., 1995, 53: 1770-1773). The break in therapy has the aim of eliminating the inhibition exerted by the progestogen on the synthesis of receptors of estradiol and progesterone and thus avoid the drop in receptiveness of hormone-dependent tissues.

20 **The progestogen** used according to the present invention is nomegestrol or one of its esters, especially nomegestrol acetate. Nomegestrol acetate is a powerful progestogen, active by the oral route, and having a novel pharmacological profile:

- in contrast to derivatives of 19-nortestosterone, nomegestrol acetate does not display any residual androgenic and estrogenic activity;
- 25 - like the derivatives of 17 $\alpha$ -hydroxyprogesterone, it has a pure pharmacological profile, but in contrast to the latter, it has a powerful antigonadotropic effect.

It belongs to the category of progestogens described as hybrids (OETTEL et al., 1999) that do not have adverse metabolic effects since the 17 $\alpha$ -ethinyl function is absent, and  
 30 that combine the advantages of the derivatives of progesterone with those of more modern derivatives of 19-nortestosterone.

Its use in sequential administration in the menopause at a dose of 5 mg/day, 12 days per cycle, in combination with various types of estrogens, makes it possible to prevent endometrial hyperplasia as shown in a multi-centre study on 150 women for 1 year (THOMAS J.L., BERNARD A.M., DENIS C., 7th International Congress on the Menopause, Stockholm, 20-24 June 1993, Abstr. 372).

Absence of hyperplasia was confirmed in a study in which nomegestrol acetate was administered at the same dose, 14 days per cycle, in women 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 use is the object of French Patent 2,737,411 in the name of the Applicant Company which claims a range of doses between 1.5 and 6 mg, preferably between 2.5 and 5 mg.

**The estrogen** used is estradiol, free or esterified, and especially estradiol valerate, or natural or synthetic conjugated estrogens or an alkynyl derivative such as ethynyl estradiol, which is presented according to an active formulation by the oral route. It was shown that a dose of estradiol between 1 and 2 mg/day made it possible to counteract estrogen deficiency in menopausal women.

Nomegestrol acetate and free or esterified estradiol, or equine conjugated estrogens, are administered in one of the forms permitting oral administration: capsules, cachets, pills, powder sachets, tablets, coated tablets, lozenges etc.

The present invention is characterized in that it comprises a new estrogen-progestogen combination, active orally, with combined administration. The present invention also relates to the use of the compositions according to the invention in the correction of estrogen deficiencies, in the prevention of osteoporosis and of cardiovascular diseases in menopausal women.

The present invention is also characterized:

a) in that it relates to an estrogen-progestogen combination different from those described previously for the same type of indications.

Some patents claim the use of estrogen-progestogen combinations continuously for replacement therapy in the menopause. This applies for example to patents US 5108995 or EP 309263. However, these patents clearly claim multisequential treatments with changes of the doses of the active ingredients. This also applies to patents filed in the USA (US 4820831 A and RE 36247) and in Europe (EP 136 011) in the name of PLUNKETT. These patents claim the use of numerous estrogens and numerous progestogens in replacement therapy in the menopause. It appears, however, that these claims do not cover the use of all the progestogens on the one hand for scientific reasons and on the other hand for scientific and legal reasons connected with the wording of the claims of these two patents:

1) The use of numerous progestogens is based on equivalences with one of them, in this case levonorgestrel. This approach does not seem admissible since the various progestogens are characterized by very different pharmacological profiles and it is not possible to deduce the doses to use by a system of simple and single equivalence. This impossibility becomes evident if we consider the ranges of active doses of different progestogens proposed in three different patents (Table 1).

It can be seen that the lower limit for the various progestogens ranges in a ratio of 2.4 to 50 whereas the upper dose ranges in a ratio of 1 to 50. Accordingly, for indications of the same type, the dose ranges vary considerably from one patent to another, which shows that the equivalence system does not lend credibility to the relationships that might be found between progestogens.

2) In addition, it might legitimately be thought that the doses claimed ought to be based on previously published and generally accepted pharmacological and/or clinical data. Now, if we consider the doses defined as in the PLUNKETT patents, it can easily be seen that, in the majority of cases, the active doses published a long time ago, i.e. before these patents were filed (NEUMANN, 1977) or more recently (KUHL, 1996), are very consistent but are only rarely within the dose ranges claimed in the patents in the name of PLUNKETT (Table 2).

This statement is also valid if we take into account, instead of the active doses as previously, the ratio between the active doses, taking norgestrel as reference (=1) (Table 3).

**Table 1**  
**Doses ( $\mu\text{g/day}$ ) of the various progestogens claimed according to the patents**

| PROGESTOGEN          | PATENT       | DOSE ( $\mu\text{g/day}$ ) |       |
|----------------------|--------------|----------------------------|-------|
|                      |              | Min.                       | Max.  |
| 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   |
| Noresthisterone      | WO 95/17194  | 350                        | 750   |
| Noresthisterone      | EP 025607 A1 | 85                         | 350   |
| Noresthisterone      | PLUNKETT     | 150                        | 1000  |
| Norethisterone Acet. | PLUNKETT     | 100                        | 1000  |
| Norgestimate         | WO 95/17194  | 200                        | 300   |
| Norgestrel           | PLUNKETT     | 50                         | 150   |
| Ethinodiol diacetate | PLUNKETT     | 100                        | 1000  |
| Dihydrogesterone     | PLUNKETT     | 5000                       | 30000 |
| MPA                  | PLUNKETT     | 1000                       | 15000 |
| Norethynodrel        | PLUNKETT     | 200                        | 5000  |
| Allylestrenol        | PLUNKETT     | 1000                       | 10000 |
| Lynestrenol          | PLUNKETT     | 100                        | 2000  |
| Quingestanol Acetate | PLUNKETT     | 50                         | 1000  |
| Medrogestone         | PLUNKETT     | 1000                       | 10000 |
| Norgestrienone       | PLUNKETT     | 20                         | 200   |
| Dimethisterone       | PLUNKETT     | 500                        | 15000 |
| Ethisterone          | PLUNKETT     | 1000                       | 25000 |
| Ciproterone Acetate  | PLUNKETT     | 100                        | 10000 |
| Ciproterone Acetate  | WO 95/17194  | 100                        | 200   |

**Table 2**  
**Doses of each progestogen according to the various bibliographical sources**

|                        | Patent US 4826831 |       | NEUMANN PUBLICATION |                  |          |                   | KUHHL    |          |
|------------------------|-------------------|-------|---------------------|------------------|----------|-------------------|----------|----------|
|                        | Min.              | Max.  | Endo (1)            | Menstruation (2) | Ovul (3) | Contraception (4) | Endo (1) | Ovul (3) |
| Levonorgestrel         | 25                | 75    |                     |                  |          |                   |          | 60       |
| Norgestrel             | 50                | 150   | 1200                | 2000             | 100      | 250               | 400      |          |
| Norethisterone         | 150               | 1000  | 12500               | 5000             | 800      | 1000              | 10000    | 400      |
| Norethisterone Acetate | 100               | 1000  |                     |                  | 800      | 1000              |          |          |
| Ethinodiol diacetate   | 100               | 1000  | 2500                |                  |          |                   |          |          |
| Dydrogesterone         | 5000              | 30000 |                     |                  |          |                   |          |          |
| MPA                    | 1000              | 15000 | 5500                | 25000            |          | 5000              |          |          |
| Norethynodrel          | 200               | 5000  | 10000               | 7500             | 6000     | 2500              |          |          |
| Allylestrenol          | 1000              | 10000 | 1750                |                  |          |                   |          |          |
| Lynestrenol            | 100               | 2000  | 1000                |                  |          | 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     |

Cases shown with grey shading correspond to active doses outside of the dose range claimed in the "PLUNKETT" patents. Dose required ( $\mu\text{g/day}$ ) for transformation of the endometrium (1), for an adequate delay in appearance of menstruation (2), for inhibition of ovulation (3), for a contraceptive effect (4)

**Table 3 : Ratios of doses of each progestogen according to the various bibliographical sources  
The reference progestogen is norgestrel (= 1)**

|                        | Patent<br>US 4826831<br>Ratio |            | NEUMANN         |               |                  |                  |
|------------------------|-------------------------------|------------|-----------------|---------------|------------------|------------------|
|                        | Min.                          | Max.       | Endometrium (1) | Ovulation (3) | Menstruation (2) | Contraception(4) |
| Levonorgestrel         | 0.5                           | 0.5        |                 |               |                  |                  |
| <b>Norgestrel</b>      | <b>1.0</b>                    | <b>1.0</b> | <b>1.0</b>      | <b>1.0</b>    | <b>1.0</b>       | <b>1.0</b>       |
| 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              |
| Ethinodiol 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             |               |                  |                  |
| Lynestrenol            | 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 with grey shading correspond to active doses outside of the range of ratios claimed in the aforementioned US and EP patents in the name of PLUNKETT(1), (2), (3), (4) : see Table 2

### Reasons connected with the claims

- 1) In the aforementioned US patents, claims 1 and 2 are oriented towards continuous treatment; the only progestogens claimed are dl-norgestrel and levonorgestrel. The subsequent claims relate to plurisquential intermittent treatment, i.e. a therapeutic regimen different from that proposed in the present patent application. For this last-mentioned type of therapeutic regimen, a larger number of progestogens is claimed, but the list is precise and limited as is clear from the version of the Markush type of the said claims of the reissue cited and it does not include nomegestrol and its esters.
- 2) The European patent only claims the continuous combined treatment; the estrogens and progestogens claimed are listed in tables given in the body of the text and are referred to in the claims. Once again, nomegestrol and its esters do not appear in the lists of progestogens that can be used. Nomegestrol acetate is characterized by a powerful progestative effect, absence of residual androgenic and estrogenic effects as well as by a powerful anti-estrogenic power that is reflected, at the level of the endometrium, by strong antimitotic activity and, in consequence, a strong atrophying effect. Accordingly, it cannot be likened to the other progestogens and to believe there is a correspondence of doses in relation to another progestogen, taken as reference, can only be erroneous. Moreover, nomegestrol acetate is characterized by very good tolerance; it does not have any action on the profile of lipids, tolerance to carbohydrates, blood pressure and coagulation factors even when it is used at higher doses than those described in the present patent application and for long-term treatments (BASDEVANT et al., 1997). This aspect is very important, since the objective that consists of using replacement therapy that is the least toxic possible, employing doses that are as low as possible, is common to all therapists. In this respect, nomegestrol acetate differs from many derivatives of 19-nortestosterone mentioned in the PLUNKETT patents, they are progestogens that have androgenic and estrogenic effects that can have consequences for the endometrium, and that also have adverse metabolic effects.

For the same reasons as those mentioned above, none of the many published works concerning continuous combined treatment in the menopause can affect the present invention because none of these publications deals with a combination of

nomegestrol acetate with an estrogen. This applies for example to combinations 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), of estradiol and medrogestone (AFFINITO et al., 1998), of estradiol and norgestrel (WOLFE and PLUNKETT, 1994), of estradiol valerate and chlormadinone acetate (RAUCH and TAUBERT, 1993), of equine conjugated estrogens with medroxyprogesterone acetate (REUBINOFF et al., 1995; WOLFE and HUFF, 1995; MIZUNUMA et al., 1997) or medrogestone (RECKER et al., 1999).

10 **b) in that it is an estrogen-progestogen combination that differs from the combination previously patented by the Applicant Company**

French Patent 2,754,179 in the name of the Applicant Company claims a combination of estradiol and nomegestrol acetate for combined replacement treatment of the menopause. The range of doses claimed on the basis of previous experience with nomegestrol acetate in sequential treatment, ranged from 1.5 to 3.75 mg, and was preferably 2.5 mg. Clinical trials on a larger scale showed, unexpectedly, that much lower doses of nomegestrol acetate, and especially from 0.1 mg to 1.00 mg, were able to ensure endometrial atrophy and very good control of bleeding. This is an important observation as it means that the doses of nomegestrol acetate can be further reduced, and therefore it becomes even safer in use.

The doses of estradiol claimed in this patent ranged from 0.2 to 3 mg. The doses of estradiol used here are somewhat different in the estrogen/progestogen ratio, i.e. 0.5/2 instead of 6:1.

25 **c) the method of manufacture of suitable pharmaceutical forms.**

The invention relates to a method of manufacture in which the two active ingredients can be combined in the same pharmaceutical form.

30 The compositions according to the invention, based on nomegestrol acetate and free or esterified estradiol, or conjugated estrogens, are administered 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 0.1 to 1.8 mg and a quantity of free or

esterified estradiol, or of conjugated estrogens, ranging from 0.5 to 2 mg. Preferably, the optimum formulations contain from 0.125 to 1.0 mg of norgestrel acetate combined with 0.5 to 1.0 mg of free estradiol or 0.5 to 1 mg of estradiol ester or 0.312 to 0.625 mg of conjugated estrogens or ethynyl estradiol, per daily dose.

5

This kind of combined administration is indicated for women who have become menopausal either naturally or through surgery; the estrogen-progestogen combination is intended to counteract the functional problems caused by estrogen deficiency of the menopause, while maintaining atrophy of the endometrium and preventing, in the majority of patients, the occurrence of withdrawal bleeding.

10

The present invention also relates to a method of production of new pharmaceutical compositions that consists of mixing the active ingredients: norgestrel or one of its esters and free or esterified or alkynylated estradiol, or conjugated estrogens with one or more inert, non-toxic, pharmaceutically acceptable excipients or vehicles.

15

Among the excipients, we may mention binders and solubilizers, compacting agents, disintegrating agents and slip agents.

This mixture can be submitted to compaction that is direct or in several stages, to form tablets that can, if desired, be provided with surface protection by covering with a film, coating or sugar-coating. The production of tablets by direct compaction permits maximum reduction of the proportion of diluents, binders, disintegrating and slip agents.

20

Capsules can be produced by mixing the active ingredients with an inert diluent and a slip agent.

25

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

30

The binders for compaction are generally microcrystalline celluloses, such as those sold under the names AVICEL PH 101 or AVICEL PH 102.

Polyvinylpyrrolidone also plays an important role, facilitating the agglomeration of powders and compaction of the mass. The polyvinylpyrrolidones used for this purpose have molecular weight between 10000 and 30000 such as Povidone, Kollidon of grade between 12 and 30.

- 5 The mixture also contains slip agents or antistatic agents which prevent agglomeration of the powder in the feed hoppers. We may mention, in this connection, colloidal silicas sold under the names AEROSIL 100 or AEROSIL 200.

The mixture also contains disintegrating agents which permit disintegration or crumbling complying with pharmaceutical standards. The following may be  
10 mentioned as useful disintegrating agents: crosslinked vinylpyrrolidone polymers such as those sold under the names Polyplasdone or Polyclar AT, carboxymethyl starches such as those sold under the names Amijel or Explotab, and crosslinked carboxymethylcelluloses such as the compound sold under the name AC-DI-SOL.

In addition, the preparation contains lubricating agents which facilitate compaction  
15 and ejection of the tablet in the tableting machines. As lubricating agents we may mention glycerol palmitostearate sold under the name Précirol, magnesium stearate, stearic acid or talc.

After compaction, the tablets can be coated to increase their storage life or make them easier to swallow.

- 20 The coating agents are either cellulosic such as cellulose phthalate (Sepifilm, Pharmacoat), or polyvinyllic of the type OPADRY PVA or Sépifilm ECL, or saccharosic such as sugar for sugar-coating of the type Sépisperse DR, AS, AP, or K (coloured).

- 25 The tablets, whether coated or not, can in addition be coloured on the surface or in the bulk, with mineral, vegetable or synthetic colorants (for example quinoline yellow lake or E 104 or iron oxides).

The proportions of the various constituents vary depending on the type of tablet to be produced.

- 30 The diluents vary from 20 to 75% of the total mass, the slip agents from 0.1 to 2% of the total mass, the compaction binders vary from 2 to 20%, polyvinylpyrrolidone from 0.5 to 15%, the disintegrating agents vary from 2 to 5.5% for crosslinked polyvinylpyrrolidone or for carboxymethyl starch, and from 2.0 to 3.0% for croscarmellose.

The quantities of lubricating agents vary depending on the nature of the agent from 0.1 to 3.0%.

The compositions according to the invention are intended to be administered once a day. However, depending on therapeutic requirements, administration can be split up (twice per day) or, conversely, repeated (two tablets per day).

The following examples illustrate the invention. They do not limit it in any way.

#### **EXAMPLE I: examples of formulations**

The combination of norgestrel acetate and estradiol is presented in the form of bare or film-coated tablets.

The mixture of ingredients can either be submitted to direct compaction, or a premix of estradiol can be produced first, then incorporating the norgestrel acetate and the rest of the excipients in dry form. The estradiol premix is made by dissolving the estradiol in an alcoholic solution of microcrystalline cellulose, PVP and lactose, followed by drying, grinding and sizing. This method is advantageous because the tablets that are manufactured starting from an estradiol premix exhibit an estradiol solution profile that is significantly improved relative to those 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 (qs 100%). It may be advantageous to add an antioxidant such as alpha-tocopherol or ascorbic acid, during production of the premix.

. The following may be mentioned as examples of premixes:

| FORMULATIONS               | in mg / 1 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          |
| <b>TOTAL, DRY</b>          | <b>82.50</b>     | <b>100.00</b> |

This premix is added to the final mixture to obtain a tablet by direct compaction. The bare, finished tablets generally weigh from 60 to 200 mg and have the following complete formula:

5

### **FORMULATIONS OF THE BARE TABLETS**

#### **Composition**

|                          | <b>In mg/per tablet</b> |
|--------------------------|-------------------------|
| - Estradiol (premix qsf) | <b>0.2 to 2.0</b>       |
| - Nomegestrol acetate    | <b>0.100 to 1.000</b>   |
| - 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 3.00           |
| - Talc                   | 0.450 to 1.500          |

10 As an example, we may mention tablets weighing 185 mg, of the following formula:

#### **Example of formulations (UF = unit formulation), tablets of 185 mg**

|    | <b>FORMULATIONS</b>                         | <b>UF mg/1 tab. 185 mg</b> | <b>UF %</b>   |
|----|---------------------------------------------|----------------------------|---------------|
| 15 | Estradiol                                   | 1.500                      | 0.811         |
|    | Nomegestrol acetate                         | <b>0.125</b>               | 0.038         |
|    | Lactose                                     | 131.790                    | 71.238        |
|    | Cellulose (Avicel PH 101)                   | 27.810                     | 15.032        |
| 20 | Povidone (K25)                              | 13.500                     | 7.297         |
|    | Precirol AT05                               | 2.780                      | 1.503         |
|    | Colloidal silica (Aerosil 200)              | 1.000                      | 0.540         |
|    | Crospovidone (Polyplasdone XL) <sup>2</sup> | 6.000                      | 3.243         |
| 25 | <b>TOTAL</b>                                | <b>185.00</b>              | <b>100.00</b> |

**Example of formulations (UF = unit formulation), tablets of 185 mg**

|    | <b>FORMULATIONS</b>            | <b>UF mg/1 tab. 185 mg</b> | <b>UF %</b>   |
|----|--------------------------------|----------------------------|---------------|
| 5  | Estradiol                      | 0.500                      | 0.270         |
|    | Nomegestrol acetate            | <b>0.125</b>               | 0.039         |
|    | Lactose                        | 136.787                    | 73.934        |
|    | Cellulose (Avicel PH 101)      | 32.813                     | 17.736        |
|    | Povidone (K25)                 | 4.500                      | 2.432         |
| 10 | Precirol AT05                  | 2.775                      | 1.500         |
|    | Colloidal silica (Aerosil 200) | 1.000                      | 0.540         |
|    | Crospovidone (Polyplasdone XL) | 6.000                      | 3.243         |
|    | <b>TOTAL</b>                   | <b>185.00</b>              | <b>100.00</b> |

**15 Example of formulations (UF = unit formulation), tablets of 120 mg**

|    | <b>FORMULATIONS</b>             | <b>UF mg/1 tab. 120 mg</b> | <b>UF %</b>   |
|----|---------------------------------|----------------------------|---------------|
| 20 | Estradiol                       | 1.500                      | 1.250         |
|    | Nomegestrol acetate             | <b>0.250</b>               | 1.042         |
|    | Lactose                         | 84.000                     | 70.000        |
|    | Cellulose (Avicel PH 101)       | 11.250                     | 9.375         |
|    | Povidone (K25)                  | 13.500                     | 11.250        |
| 25 | Silice colloïdale (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         |
|    | <b>TOTAL</b>                    | <b>120.00</b>              | <b>100.00</b> |

30

**Example of formulations (UF = unit formulation), tablets of 120 mg**

|    | <b>FORMULATIONS</b>       | <b>UF mg/1 tab. 120 mg</b> | <b>UF %</b> |
|----|---------------------------|----------------------------|-------------|
| 35 | Estradiol                 | 0.500                      | 0.417       |
|    | Nomegestrol acetate       | <b>0.250</b>               | 0.021       |
|    | 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         |
| 5 | Talc                             | 1.000         | 0.833         |
|   | Stearic acid AC/50VG (vegetable) | 2.500         | 2.083         |
|   | <b>TOTAL</b>                     | <b>120.00</b> | <b>100.00</b> |

10 **Example of formulations (UF = unit formulation), tablets of 80 mg**

|    | FORMULATIONS                   | UF mg/1 tab. 80 mg | UF %          |
|----|--------------------------------|--------------------|---------------|
|    | Estradiol                      | 0.500              | 0.625         |
| 15 | Nomegestrol acetate            | <b>0.250</b>       | 0.081         |
|    | 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         |
| 20 | Talc                           | 0.700              | 0.875         |
|    | Colloidal silica (Aerosil 200) | 0.440              | 0.550         |
|    | Magnesium stearate (vegetable) | 0.700              | 0.875         |
| 25 | <b>TOTAL</b>                   | <b>80.0</b>        | <b>100.00</b> |

**Example of formulations (UF = unit formulation), tablets of 80 mg**

|    | FORMULATIONS                   | UF mg/1 tab. 80 mg | UF %         |
|----|--------------------------------|--------------------|--------------|
| 30 | Estradiol                      | 1.000              | 1.250        |
|    | Nomegestrol acetate            | <b>0.250</b>       | <b>1.563</b> |
|    | Kollidon 25                    | 9.000              | 11.250       |
|    | Lactose M                      | 54.110             | 67.637       |
| 35 | 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         |
| <b>TOTAL</b>                   | <b>80.00</b> | <b>100.00</b> |

These tablets can be film-coated with, for example:

- 5        - film-coating agents based on polyvinyl alcohol of the type OPADRY PVA "moisture barrier" (polyvinyl alcohol, titanium dioxide, purified talc, lecithin, xanthan gum, pigments, lacquers),
- or
- 10       - film-coating agents based on cellulose of the type SEPIFILM L.P. [H.P.M.C. (hydroxypropylmethylcellulose)], microcrystalline cellulose, stearic acid, pigments, lacquers).

## Example II

### 15    **Dissociation of the antimitotic and differentiating effects of nomegestrol acetate on the endometrial cell**

Women who were menopausal, either naturally or as a result of surgery, underwent sequential estrogen-progestogen treatment. They received 30 µg of ethinyl estradiol from D1 to D12, then from the 13th to the 22nd day they received the same dose of ethinyl estradiol combined with various 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<br>10 |
| chlormadinone acetate, mg : | 0.1 |      | 0.5 | 1 | 2 |     | 5 | and<br>10 |

25

The number of women was between 2 and 11 depending on the groups.

There was then a therapeutic pause of 7 days, followed by a 2nd treatment cycle.

30    The parameters taken into account were:

- the delay in occurrence of menstruation after stopping treatment after the 1st and the 2nd treatment cycle;

- the histologic appearance of the endometrium on biopsy between the 17th and the 20th day of the second cycle.

The results show that:

- 5 • the time for appearance of menstruation depends on the dose and is similar for the 2 products. The dose necessary to prevent appearance of menstruation before the end of treatment is between 0.2 and 0.3 mg/day for both products (Table 1);
- 10 • transformation of the endometrium into secretory endometrium is complete with both products starting from 1 mg/day; it decreases for the highest doses (10 mg/day);
- 15 • proliferation activity, expressed by the number of mitoses in the gland cells, appears to be more strongly inhibited by nomegestrol acetate than by chlormadinone acetate. Mitosis no longer occurs in women treated with a dose equal to or greater than 0.5 mg/day of nomegestrol acetate whereas mitoses are still present with a daily dose of 1 mg/day of chlormadinone acetate (Table 2).

20 We can therefore conclude that at the level of the endometrium, nomegestrol acetate and chlormadinone acetate are not comparable: the activity of secretory transformation is comparable but nomegestrol acetate is characterized by very strong antimitotic and antiproliferative activity.

**Table 1 : Delay in occurrence of menstruation (days) after cessation of treatment**

| Progestogen           | Dose (mg/day)  |                |              |              |              |              |              |              |
|-----------------------|----------------|----------------|--------------|--------------|--------------|--------------|--------------|--------------|
|                       | 0.1            | 0.25           | 0.5          | 1.0          | 2.0          | 2.5          | 5            | 10           |
| Nomegestrol acetate   | - 0.5<br>± 1.5 | - 0.5<br>± 0.5 | 1.5<br>± 0.5 | 2.7<br>± 0.2 |              | 3.2<br>± 0.2 | 4.3<br>± 0.4 | 3.8<br>± 0.8 |
| Chlormadinone acetate | - 2.3<br>± 0.5 |                | 2.0<br>± 0.6 | 3.0          | 3.8<br>± 0.3 |              | 5.5<br>± 1.5 | 5.5<br>± 0.5 |

**5 Table 2 : Evaluation of the number of mitoses  
(% of section with mitoses 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  |

### 10 **EXAMPLE III**

A study was conducted for testing the effects on the endometrium of the continuous combined combination of a dose of oral estradiol equivalent to 1.5 mg and several doses of nomegestrol acetate.

This consisted of treating, for 6 consecutive months, 179 women who had been menopausal for at least 3 years, with 1.5 mg per day of estradiol combined continuously with 5 different doses of norgestrel acetate: 5 mg/day (n = 47); 2.5 mg/day (n = 42); 1.25 mg/day (n = 43); 0.625 mg/day (n = 47) and 0.125 mg/day (n = 47).

The effect of these 5 combinations on the endometrium was evaluated by collecting the characteristics of genital bleeds, measuring the thickness of the endometrium by endovaginal ultrasound scanning before and at the end of treatment and by performing a biopsy of the endometrium before and at the end of treatment.

The percentage of the women not presenting any genital bleeding during the entire treatment was respectively 40 - 42.5 - 58.1 - 52.4 and 68.1%, with doses of 0.125 - 0.625 - 1.25 - 2.5 and 5 mg of norgestrel acetate per day. The percentages observed are not statistically different between groups, but the relation between dose and incidence of bleeding is significant.

The accompanying tables show, for each dose of norgestrel acetate, the results of ultrasound scans and biopsy of the endometrium carried out at the end of the 6 months of treatment.

At the end of treatment, the average thickness of the endometrium is not different between the groups. The increase in endometrial thickness under treatment is 0.39 mm on average with the lowest dose of norgestrel acetate. This thickening increases slightly with the dose, reaching 1.56 mm in the group of women receiving 5 mg/day of progestogen, but the relation between the change in thickness and the change in dose does not reach the threshold of statistical significance.

The biopsies of the endometrium examined at the end of the study did not reveal any proliferative or hyperplastic aspect of the uterine mucosa. The highest percentage of secretory endometria was observed in women who received the highest dose of progestogen; it decreases progressively and statistically significantly with the dose. On the other hand, the highest percentage of atrophic endometria was found with the lowest dose of progestogen and it decreases with the dose.

These results are unexpected in that they show that very low doses of nomegestrol acetate administered in continuous combined form with an estrogen are able to prevent growth of the uterine mucosa and keep it in a state of atrophy whereas, in contrast to higher doses, they are insufficient to cause secretory transformation of the endometrium.

This study thus reveals a surprising decoupling of the anti-estrogen effect and of the progestative effect of nomegestrol acetate, administered in continuous combined form with estrogens.

The anti-estrogen effect is dominant since it can be detected when the progestogen, administered continuously with an estrogen, is given at low doses. These doses are insufficient to give rise to secretory transformations of the uterine mucosa. At higher doses and with the same therapeutic regimen, the secretory effect predominates, though without permitting excessive proliferation of the endometrium.

**Table I – Endometrial thickness after 6 months of continuous treatment with various combinations based on estradiol (2 mg of estradiol valerate) and of norgestrel acetate (NOMAC) at various doses**

| Doses of NOMAC<br>(mg/day)                               | 0.125<br>(n = 35) | 0.625<br>(n = 35) | 1.25<br>(n = 33) | 2.5<br>(n = 34) | 5<br>(n = 41)  |
|----------------------------------------------------------|-------------------|-------------------|------------------|-----------------|----------------|
| Mean thickness at end of<br>treatment (mm)               | 0.00<br>(1.5)     | 3.18<br>(1.65)    | 4.05<br>(3.75)   | 3.93<br>(2.10)  | 3.83<br>(2.72) |
| Average increase in<br>thickness under<br>treatment (mm) | 0.35<br>(1.7)     | 0.39<br>(1.67)    | 1.12<br>(3.67)   | 1.36<br>(1.54)  | 1.57<br>(2.39) |

( ) = standard deviation

**Table 2 – Histologic appearance of the endometrium after 6 months of continuous treatment with various combinations containing oestradiol (2 mg estradiol valerate) and of norgestrel acetate (NOMAC) at various doses**

| Doses of NOMAC<br>(mg/day) | 0.125<br>(n = 35) | 0.625<br>(n = 32) | 1.25<br>(n = 33) | 2.5<br>(n = 34) | 5<br>(n = 40) |
|----------------------------|-------------------|-------------------|------------------|-----------------|---------------|
| No endometrium             | 5<br>(16.0)       | 5<br>(15.6)       | 10<br>(30.3)     | 3<br>(8.8)      | 3<br>(7.5)    |
| Atrophic endometrium       | 24<br>(59.0)      | 19<br>(59.4)      | 10<br>(30.3)     | 8<br>(23.5)     | 3<br>(7.5)    |
| Secretory endometrium      | 7<br>(25.0)       | 8<br>(25.0)       | 12<br>(36.4)     | 22<br>(64.7)    | 34<br>(85.0)  |
| Polyp                      | 0                 | 0                 | 1<br>(3.0)       | 1<br>(2.9)      | 0             |

( ) = percentage      No endometrial proliferation or hyperplasia

## CLAIMS

1. Pharmaceutical hormonal compositions, characterized in that they are formed from an estrogen-progestogen combination intended for oral administration and permitting the simultaneous administration of an estrogen component at a dose ranging from 0.5 to 2 mg, and a progestogen component derived from 19-norprogesterone at a dose ranging from 0.1 to 1.8 mg, combined with or mixed with one or more non-toxic, inert, pharmaceutically acceptable excipients.
2. Estrogen-progestogen compositions according to claim 1, in which the estrogen component is free, esterified or alkynylated  $17\beta$ -estradiol or conjugated estrogens.
3. Estrogen-progestogen compositions according to claim 2, in which the estrogen component is  $17\beta$ -estradiol.
4. Estrogen-progestogen compositions according to claim 2, in which the estrogen component is an estradiol ester, for example estradiol valerate.
5. Estrogen-progestogen compositions according to claim 2, in which the estrogen component consists of natural or synthetic conjugated estrogens.
6. Estrogen-progestogen compositions according to claim 2, in which the estrogen component is ethynyl estradiol.
7. Estrogen-progestogen compositions according to one of the claims 1 to 6, in which the estradiol, the estradiol ester, or the conjugated estrogen, is present at a dose ranging from 0.5 to 2 mg per unit dose.
8. Estrogen-progestogen compositions according to claim 3, in which the free estradiol is present preferably at a dose of 0.5 to 1.0 mg per unit dose.

9. Estrogen-progestogen compositions according to claim 4, in which the estradiol ester is present preferably at a dose of 0.5 to 1 mg per unit dose.
- 5 10. Estrogen-progestogen compositions according to claim 5, in which the natural or synthetic conjugated estrogen is present preferably at a dose of 0.312 to 0.625 mg per unit dose.
- 10 11. Estrogen-progestogen compositions according to claims 1 to 10, in which the progestogen component is norgestrol or one of its esters.
12. Estrogen-progestogen compositions according to claim 11, in which the progestogen component is norgestrol acetate.
- 15 13. Estrogen-progestogen compositions according to claims 11 and 12, in which the norgestrol acetate is present at a dose ranging from 0.1 to 1.0 mg per unit dose.
- 20 14. Estrogen-progestogen compositions according to claims 11 to 13, in which the norgestrol acetate is present at a dose between 0.125 and 1.00 mg per unit dose.
- 25 15. Use of the estrogen-progestogen mixture according to one of the claims 1 to 14, for production of a drug intended for the treatment of estrogen deficiencies in menopausal women.
16. Use of the estrogen-progestogen mixture according to one of the claims 1 to 14, for production of a drug intended for preventing osteoporosis and cardiovascular diseases in menopausal women.
- 30 17. Use of the estrogen-progestogen mixture according to one of the claims 1 to 14, for production of a drug intended to be administered continuously or intermittently.

18. A method of preparation of novel estrogen-progestogen compositions according to one of the claims 1 to 14, in which the estrogenic active principle and the progestative active principle are mixed or incorporated with one or more inert, non-toxic, pharmaceutically acceptable excipients.