

REPUBLIC OF SOUTH AFRICA

PATENTS ACT, 1978

PUBLICATION PARTICULARS AND ABSTRACT

(Section 32(3)(a) – Regulations 22(i)(g) and 31)

OFFICIAL APPLICATION NO.		LODGING DATE		ACCEPTANCE DATE	
21	01	23	22 March 2006	43	5.2.07
2006/02338					
INTERNATIONAL CLASSIFICATION			NOT FOR PUBLICATION		
51	A61K		CLASSIFIED BY :		
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EARLIEST PRIORITY CLAIMED		COUNTRY		NUMBER		DATE	
NOTE : the country must be indicated by its International Abbreviation – see Schedule 4 of the Regulations		33	DK	31	PA 2003 01408	32	29 September 2003

TITLE OF INVENTION	
54	IMPROVED STABILITY OF PROGESTOGEN FORMULATIONS

57	ABSTRACT (NOT MORE THAN 150 WORDS)	NUMBER OF PAGES	32
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FOR ABSTRACT SEE THE NEXT SHEET

2006/02338

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau(43) International Publication Date
7 April 2005 (07.04.2005)

PCT

(10) International Publication Number
WO 2005/030176 A1

(51) International Patent Classification: A61K 9/20

(21) International Application Number: PCT/DK2004/000639

(22) International Filing Date:
21 September 2004 (21.09.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PA 2003 01408 29 September 2003 (29.09.2003) DK
60/509,962 9 October 2003 (09.10.2003) US(71) Applicant (for all designated States except US): NOVO
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Allé, DK-2880 Bagsvaerd (DK).(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AI, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, GR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
ZW(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI,
SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).**Published:**

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

For two-letter codes and other abbreviations, refer to the "Guid
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: IMPROVED STABILITY OF PROGESTOGEN FORMULATIONS

(57) Abstract: In a preparation for hormone replacement therapy having a low content of progestogen, the stability of the pro-
gestogen component can be enhanced by using a cellulosic binder, for example hydroxypropylcellulose, instead of a non-cellulosic
binder

WO 2005/030176 A1

IMPROVED STABILITY OF PROGESTOGEN FORMULATIONS

Field of this Invention

5 The present invention relates to progestogen-containing pharmaceutical formulations.

Background of this Invention

10 Progestogens have wide use as therapeutic agents, such as, for example, in hormone replacement therapy, and as components of contraceptives and for the treatment of osteoporosis. Nonetheless, with an increasing awareness of the risks involved with various types of combined estrogen/progestogen administration, there have been increased efforts to formulate products that deliver lower dosages of these hormones. Unfortunately, lowering the concentration of a steroid component in a formulation may result in some degree of lowered stability and/or recoverability of the component.

15 Examples of documents defining the general state of the art are the following patents and patent applications: EP 337,938 A2; EP 787,488 A1; EP 1,334,724 A1; US 5,770,227; US 6,284,263 B1; US 2002/0168412 A1; and US 2003/0077297 A1.

Thus, there is a need in the art for improved formulations containing progestogens that exhibit acceptable stability of the progestogen component.

20 Hence, one object of this invention is to provide a formulation containing progestogen in low amount which has a satisfactory high stability.

Summary of this Invention

25 The present invention provides pharmaceutical formulations comprising (i) a progestogen and (ii) a cellulosic binder, comprising not more than about 1.5% (weight/weight (hereinafter designated w/w)) norethisterone acetate (hereinafter designated NETA) relative to the total formulation, such as, for example, from about 0.05% to about 1.5% (w/w) NETA or the equivalent amount of a non-NETA progestogen. In different embodiments, the formulation may comprise less than about 0.75%, about 0.5%, about 0.25%, or about 0.1% (w/w) NETA relative to the total formulation, such as, for example, between about 0.05-0.75%; 0.05-0.5%; 0.05-0.25%; 0.05-1.5%; 0.1-0.75%; 0.1-0.5%; 0.1-0.25%; 0.25-0.75%; 0.25-0.5%, NETA or the equivalent amount of a non-NETA progestogen. In another aspect, the invention provides pharmaceutical formulations comprising (i) a progestogen and (ii) a cellulosic binder, comprising not more than 0.5 mg NETA per unit dosage form, including, without limitation, not more than 0.4, 0.3, 0.25, 0.2, 0.1, or 0.05 mg NETA per unit dosage form, such

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as, for example, between about 0.05-0.5 mg; 0.05-0.4 mg; 0.05-0.3 mg; 0.05-0.25 mg; 0.05-2.0 mg; 0.05-0.1 mg; 0.1-5 mg; 0.1-0.4 mg; 0.1-0.3 mg; 0.1-0.25 mg; and 0.1-0.2 mg NETA or the equivalent amount of a non-NETA progestogen. In these embodiments, typically, the unit dosage form is a pellet, tablet or capsule having a total weight (excluding capsule or coating) of between about 25 and 125 mg.

Preferably, the stability of the progestogen component is enhanced relative to the stability of progestogen in a parallel formulation in which the non-cellulosic binder is replaced with an equivalent amount of a cellulosic binder. In one series of embodiments, the stability of the progestogen component is enhanced relative to the stability of progestogen in a parallel formulation in which the polyvinylpyrrolidone is replaced with an equivalent amount of hydroxypropylcellulose. In another series of embodiments, the stability of the progestogen component is enhanced relative to the stability of progestogen in a parallel formulation in which the gelatin is replaced with an equivalent amount of hydroxypropylcellulose.

Non-limiting examples of suitable cellulosic binders for use in the present invention include methylcellulose, sodium carboxymethylcellulose (for example Tylose™), ethylcellulose (for example Ethocel™), hydroxypropyl methyl cellulose (HPMC) (Shin-Etsu Chemical Co., Ltd.), and hydroxypropyl cellulose (for example Klucel™).

In some embodiments, the formulation has the composition stated in table I below:

Table I

Estradiol hemihydrate	about 0.5 mg
Norethisterone Acetate	about 0.1 mg
Lactose monohydrate	about 37 mg
Maize starch	about 37 mg
Hydroxypropyl cellulose or hydroxypropyl methyl cellulose	about 3 mg
Talc	about 0.8 mg
Magnesium stearate	about 0.4 mg

In another aspect, the invention provides methods for stabilizing a progestogen component of a pharmaceutical formulation, particularly a formulation in which NETA is present at a concentration not more than about 1.5% w/w relative to the total formulation (such as, for example, between about 0.05-1.5% w/w) or a formulation in which NETA is present in an amount not more than about 0.5 mg per unit dosage form or the equivalent amount of a non-NETA progestogen. The methods are carried out by contacting the progestogen with a stabilizing-effective amount of a cellulosic binder. A stabilizing-effective amount is an amount of

binder that enhances the shelf-life of the progestogen component. The stability of a formulation according to this invention can be determined by comparing the stability of progestin in said formulation with the stability of progestin in an identical formulation which deviates only in that the cellulosic binder has been exchanged by an identical amount of polyvinylpyrrolidone. Conveniently, such tests are performed at a temperature of 40°C and a relative humidity of 75% and analyses for stability are made after 0, 3, and 6 months. Conveniently, the stability is enhanced by about 5% or more.

In another aspect, the invention provides methods for treating a progestogen-responsive syndrome, which are carried out by administering to a patient in need of such treatment an effective amount for treating the syndrome of a formulation of the invention.

Detailed Description of the Invention

The present invention relates to improved formulations of progestogen-containing medications. Such formulations can, for example, be administered orally, vaginally, or transdermally. The present inventor has found that the use of one or more cellulosic binders in progestogen-containing formulations provides superior stability and/or recoverability of the active ingredient relative to conventional formulations, particularly when the formulation contains NETA at a concentration not more than about 1.5% w/w relative to the total weight of the composition, such as, for example, not more than about 0.5 mg NETA or the equivalent amount of a non-NETA progestogen in a conventional unit dosage form such as a tablet or capsule. In some embodiments, the content of NETA in the formulation is not more than about 0.75%, 0.5%, 0.25%, or 0.1% w/w relative to the total formulation, such as, for example, between about 0.05-0.75%, 0.05-0.5%, 0.05-0.25%, 0.05-1.5%; 0.1-0.75%; 0.1-0.5%; 0.1-0.25%; 0.25-0.75%; 0.25-0.5% w/w NETA or the equivalent amount of a non-NETA progestogen. In some embodiments, the content of NETA in the formulation is less than about 0.4 mg/unit dosage form, including, without limitation, not more than about 0.3, 0.25, 0.2, and 0.1 mg NETA/unit dosage form, such as, for example, between about 0.05-0.5 mg; 0.05-0.4 mg; 0.05-0.3 mg; 0.05-0.25 mg; 0.05-2.0 mg; 0.05-0.1 mg; 0.1-0.5 mg; 0.1-0.4 mg; 0.1-0.3 mg; 0.1-0.25 mg; and 0.1-0.2 mg NETA per unit dosage form or the equivalent amount of a non-NETA progestogen.

Stability and/or recoverability as used herein refers to the ability to detect the progestogen active ingredient in a formulation, typically by HPLC, after a storage interval under predetermined conditions of temperature and humidity (see, for example, Example 1 below.)

Progestogen as used herein includes any drug that binds to the progestogen receptor and induces a progestational effect. Progestogens include, without limitation, all of the

known progestogens and derivatives of progesterone or testosterone that have progestogen activity. The known synthetic progestogens are mainly derivatives of 17α -hydroxyprogesterone or 19-nortestosterone. These progestogens can be classified into three groups: the pregnane, estrane, and gonane derivatives. The pregnane progestogens, derived from 17α -hydroxyprogesterone, include, for example, medroxyprogesterone acetate, chlormadinone acetate, megestrol acetate, and cyproterone acetate. The estranes, derived from 19-nortestosterone include norethindrone, norethynodrel, lynestrenol, norethindrone acetate (NETA), ethynodiol acetate, and norethindrone enanthate. The gonanes are derived from the basic estrane structure, with the addition of an ethyl group of position 13 of the molecule. Drugs in this group include, for example, norgestrel (-dextro and -laevo), norgestimate, desogestrel, and gestodene. Additional non-limiting examples of progestogens include osaterone, dienogest, chlormadinone acetate, and drospirenone.

One way of determining which amount of a non-NETA progestogen is equivalent with NETA is to determine the amount which gives the same action on the endometrium. This could be designated an endometrium transformation dosage. Assessment of the potency of orally administered progesterones in women can be made as described in *Fertility and Sterility* 46 (1986), 1062 *et seq.* Examples of endometrium transformation dosages are 1 mg NETA = 5 mg medroxyprogesterone acetate and 1 mg NETA = 1 mg cyproterone acetate. Other figures are known from the literature.

Progestogens may be formulated as pharmaceutically acceptable salts, including, without limitation, organic acid addition salts formed with acids which form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartrate, succinate, benzoate, ascorbate, α -ketoglutarate, and α -glycerophosphate. Suitable inorganic salts may also be formed, including, without limitation, hydrochloride, sulfate, nitrate, bicarbonate, and carbonate salts.

In a preferred embodiment of this invention, the progestogen is a 19-nortestosterone derivative, preferably norgestrel, laevonorgestrel, NET or NETA.

In another preferred embodiment of this invention, the progestogen is a soluble ester or salt of norethindrone, preferably a soluble ester, more preferred NETA or norethindrone enanthate.

In a further preferred embodiment of this invention, the progestogen is NETA.

In practicing the present invention, a progestogen-containing formulation is prepared by contacting the progestogen with a cellulosic binder. The binder may comprise, without limitation, one or more of methylcellulose, sodium carboxymethylcellulose (for exam-

ple Tylose™), ethylcellulose (for example Ethocel™), hydroxypropyl methyl cellulose (HPMC) (Shin-Etsu Chemical Co., Ltd.), and hydroxypropyl cellulose (for example Klucel™). For tablet formulations, binders impart sufficient cohesion to the powders to permit normal processing such as sizing, lubrication, compression, film coating, and packaging, but still permit the tablet to disintegrate and the composition to dissolve upon ingestion. In the present invention, the cellulosic binders also impart enhanced stability and/or recoverability to the progestogen active ingredient. Typically, the progestogen-containing formulations of the invention comprise one or more cellulosic binders in the range of about 0.5% to about 25%, such as, for example, about 0.75% to about 15% or about 1.5% to about 10%, of the total weight of the unit dosage form.

According to one embodiment of this invention, the cellulosic binder is hydroxypropyl cellulose having a molecular weight in the range from about 30,000 to about 1,500,000, preferably in the range from about 50,000 to about 150,000.

According to one embodiment of this invention, the cellulosic binder is hydroxypropyl cellulose, preferably hydroxypropyl cellulose fulfilling the requirements of European Pharmacopoeia and/or the United States National Formulary.

In one embodiment of the invention, the progestogen is NETA, the binder is Klucel™, and the unit dosage form is a tablet containing about 0.1 to about 0.25 mg NETA and about 3.2 mg Klucel™ (total tablet weight = 80-85 mg).

The formulations of the invention may optionally comprise one or more diluents. Suitable diluents include, without limitation, either individually or in combination, lactose USP; lactose USP, anhydrous; lactose USP, spray dried; starch USP; directly compressible starch; mannitol USP; sorbitol; dextrose monohydrate; microcrystalline cellulose NF; dibasic calcium phosphate dihydrate NF; sucrose-based diluents; confectioner's sugar; monobasic calcium sulfate monohydrate; calcium sulfate dihydrate NF; calcium lactate trihydrate granular NF; dextrates NF (for example, Emdex™); Celutab™; dextrose (for example, Cerelease™); inositol; hydrolyzed cereal solids such as the Maltrons™ and Mor-Rex™; amylose; Rexcel™; calcium carbonate; glycine; bentonite; and the like. The formulations typically comprise one or more diluents in the range of about 5% to about 99%, preferably about 25% to about 90%, and more preferably about 40% to about 80%, of the total weight of the composition.

The formulations of the invention may optionally comprise one or more disintegrants, particularly for tablet formulations. Suitable disintegrants include, without limitation, either individually or in combination, starches; sodium starch glycolate; clays (such as Veegum™HV); alginates; pregelatinized corn starches (such as National™ 1551 and National™ 1550); and gums (such as agar, guar, locust bean, Karaya™, pectin, and tragacanth).

Disintegrants can be added at any suitable step during the preparation of the pharmaceutical composition, particularly prior to granulation or during the lubrication step prior to compression. The present pharmaceutical compositions comprise one or more disintegrants in the range of about 5% to about 99%, preferably about 25% to about 90%, and more preferably about 40% to about 80%, of the total weight of the composition.

The formulations of the invention optionally comprise one or more lubricants and/or glidants as a carrier material. Suitable lubricants and/or glidants include, without limitation, either individually or in combination, such lubricants and/or glidants as glyceryl behenate (CompritolTM 888); metallic stearates (for example, magnesium, calcium and sodium stearates); stearic acid; hydrogenated vegetable oils (for example, SterotexTM); talc; waxes; StearowetTM; boric acid; sodium benzoate and sodium acetate; sodium chloride; DL-Leucine; polyethylene glycols (for example, CarbowaxTM 4000 and CarbowaxTM 6000); sodium oleate; sodium benzoate; sodium acetate; sodium lauryl sulfate; sodium stearyl fumarate (Pruv.TM.); and magnesium lauryl sulfate. The present pharmaceutical compositions comprise one or more lubricants at about 0.1% to about 10%, preferably about 0.2% to about 8%, and more preferably about 0.25% to about 5%, of the total weight of the composition. Magnesium stearate is a preferred lubricant used to reduce friction between the equipment and granulation during compression.

Talc is a preferred anti-adherent or glidant agent used to reduce sticking to equipment surfaces and also to reduce static in the blend. The compositions preferably comprise talc at about 0.1% to about 10%, more preferably about 0.25% to about 5%, and still more preferably about 0.5% to about 2%, of the total weight of the composition.

The formulations of the invention optionally comprise one or more wetting agents, particularly for tablet formulations. Suitable wetting agents include, either individually or in combination, such wetting agents as oleic acid; glyceryl monostearate; sorbitan monooleate; sorbitan monolaurate; triethanolamine oleate; polyoxyethylene sorbitan mono-oleate; polyoxyethylene sorbitan monolaurate; sodium oleate; and sodium lauryl sulfate. Wetting agents that are anionic surfactants are preferred. The formulations of the invention typically comprise one or more wetting agents present at about 0.1% to about 15%, preferably about 0.25% to about 10%, and more preferably about 0.5% to about 5%, of the total weight of the composition.

Other carrier materials (such as colorants, flavors and sweeteners) and modes of administration are known in the pharmaceutical art and can be used in the preparation of the formulations of the present invention.

In one preferred embodiment, the formulation according to this invention has a loss of mass (w/w) of not more than 15%, preferably of not more than 10 %, when tested according to European Pharmacopoeia 4th edition 2002, item 2.2.32, test C.

5 In another preferred embodiment, the formulation according to this invention disintegrates within 2 hours, preferably 1 hour, more preferred 30 minutes, most preferred 15 minutes when tested by the method described in European Pharmacopoeia 4th edition 2002, item 2.9.1, test A.

10 ***Dosage forms and coatings***

A dosage form, as used herein, refers to a formulation that is ready for administration to a subject. In practicing the present invention, progestogen-containing compositions may be formulated as tablets, pills, hard or soft capsules, lozenges, cachets, dispensable powders, granules, beadlets, pellets, suspensions, elixirs, and the like. The invention also encom-
15 passes multilayered tablets wherein a given layer may represent a different drug, as well as powders, pellets and granules that are encapsulated. The powders, pellets, and granules may be coated with a suitable polymer or a conventional coating material to achieve, for example, greater stability in the gastrointestinal tract, to achieve the desired rate of release, or to achieve a product with improved stability. Moreover, the capsule comprising the powder,
20 pellets or granules may be further coated. The tablet or the caplet may also be scored to facilitate division of dosing. Alternatively, the dosage forms of the present invention may be unit dosage forms wherein the dosage form is intended to deliver one therapeutic dose per administration.

Preferably, the composition is formulated into a discrete dosage unit containing a
25 predetermined amount of the active ingredients, such as tablets or capsules. Unit dosage tablets or capsules are preferred.

Coatings typically comprise one or more compounds that form a film, as well as one or more plasticizers.

Film-forming compounds include, without limitation, cellulosic compounds such as,
30 for example, hydroxypropyl methyl cellulose, ethylcellulose, methacrylates, cellulose acetate phthalates, polyvinyl acetate phthalates, waxes, and silicone elastomers.

In a preferred embodiment, the cellulosic coating is selected from the group consisting of methylcellulose, sodium carboxymethylcellulose, preferably Tylose™, ethylcellulose, preferably Ethocel™, hydroxypropyl methyl cellulose (herein designated HPMC), and hy-
35 droxypropyl cellulose, preferably Klucel™.

Plasticizers include, without limitation, glycerin, glycerol triacetate, propylene glycol, polyethylene glycol, triacetin, triethyl citrate, acetylated monoglycerides MACROGOL 6,000, and the like.

In one aspect, the invention provides progestogen-containing tablets coated with
5 1.5-5% w/w of a cellulosic film-forming compound relative to the total weight of the tablet, such as, for example, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5, and 5% w/w. In these embodiments, the progestogen content of the formulation is (i) not more than about 0.75%, 0.5%, 0.25%, or 0.1% w/w relative to the total formulation, such as, for example, between about 0.05-0.75%, 0.05-0.5%, 0.05-0.25%, 0.05-1.5%; 0.1-0.75%; 0.1-0.5%; 0.1-0.25%; 0.25-
10 0.75%; 0.25-0.5% w/w, and the like, or (ii) less than about 0.4 mg/tablet, including, without limitation, not more than about 0.3, 0.25, 0.2, and 0.1 mg progestogen/tablet, such as, for example, between about 0.05-0.5 mg; 0.05-0.4 mg; 0.05-0.3 mg; 0.05-0.25 mg; 0.05-2.0 mg; 0.05-0.1 mg; 0.1-0.5 mg; 0.1-0.4 mg; 0.1-0.3 mg; 0.1-0.25 mg; and 0.1-0.2 mg per tablet.

In one embodiment, the formulation is a tablet containing 0.1-0.25 mg NETA and
15 3.2 mg Klucel™ (total tablet weight = 80-85 mg) and coated with 3% methylhydroxypropyl-cellulose E3 (total weight about 2.3 mg/tablet).

The formulations of the invention may be manufactured using conventional means of granulation and tableting, including, without limitation, wet granulation and tableting followed by film-coating or direct compression followed by film-coating.

20 Typically, the tablet process comprises the steps of preparing granules suitable for tableting by blending a mixture comprising the medicament, a binder, and optionally, a disintegrant and filler; adding a predetermined amount of water or granulation fluid to form a wet mass blend; sizing the wet mass blend into granules to aid drying; drying the wet granules to remove excess moisture; sizing the dried granules into granules suitable for tableting, and
25 adding lubricant, one or more fillers, one or more dry binders, optionally a disintegrant, and other excipients necessary for tableting the granules; and a film-coating step.

Methods for preparing the formulations of the invention are well-known in the art and can be found, for example, in Remington, 19th Edition, Vol. II, Chapter 92, (Mack Publishing Company, Easton PA, 1995).

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Other active ingredients

In addition to progestogen, the formulations of the invention may comprise one or more additional active ingredients, including, without limitation, an estrogen, a second progestogen product, an androgenic agent, an androgen agonist, a progestogen agonist, an estrogen antagonist, or another hormone product. Estrogen, for example, may include, without limitation,
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ethinyl estradiol, mestranol, conjugated equine estrogen, estrone, estradiol, esterified estrogens, estropipate, and other estrogen equivalents and estrogen agonists.

In one embodiment, the formulation is a tablet containing 0.5 mg estradiol in addition to 0.1 or 0.25 mg NETA.

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Methods of stabilization

The present invention also provides methods for stabilizing a progestogen active ingredient in a pharmaceutical composition, particularly a dry composition such as, for example, a tablet, in which the progestogen is present in a proportion of not more than 1.5% w/w relative to the total weight of the composition, which are carried out by contacting the progestogen with a cellulosic binder such that the cellulosic binder comprises between about 0.5% to about 25%, such as, for example, about 0.75% to about 15% or about 1% to about 10%, of the total weight of the composition. Non-limiting examples of suitable cellulosic binders include methylcellulose, sodium carboxymethylcellulose (for example Tylose™), ethylcellulose (for example Ethocel™), hydroxypropyl methyl cellulose (HPMC) (Shin-Etsu Chemical Co., Ltd.), and hydroxypropyl cellulose (for example Klucel™). However, it will be understood that any cellulosic binder may be used that imparts enhanced stability and/or recoverability to the formulation. Typically, use of a cellulosic binder in a dilute progestogen formulation according to the present invention results in an enhancement of at least about 5%, preferably about 10%, more preferably about 25%, and most preferably about 50%, in one or more parameters of stability/recoverability.

A typical parameter of stability/recoverability (as recommended by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) is shelf life, which is defined as the time period during which a drug product is expected to remain within the approved shelf life specification. The ICH guidelines provide that accelerated testing may be performed for a 6-month period at 40°C/75% relative humidity, and that a significant change in drug concentration is about 5% from the initial assay values under accelerated testing conditions. In one series of embodiments, the stability of the progestogen component is enhanced relative to the stability of progestogen in a parallel formulation in which the polyvinylpyrrolidone is replaced with an equivalent amount of hydroxypropylcellulose. In another series of embodiments, the stability of the progestogen component is enhanced relative to the stability of progestogen in a parallel formulation in which the gelatin is replaced with an equivalent amount of hydroxypropylcellulose. In these two last-mentioned tests, the stability of the progestogen component is enhanced at least 5%, preferably at least 10%, more preferred at least 15 %.

In another aspect, the present invention also provides methods for stabilizing a progestogen active ingredient in a pharmaceutical composition, particularly a dry composition such as, for example, a tablet, in which the progestogen is present in a proportion of not more than 1.5% w/w relative to the total weight of the composition, which methods are carried out by coating the progestogen-containing dosage form with 0.5-5% w/w of a cellulosic film-forming compound relative to the total weight of the tablet, such as, for example, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5, and 5% w/w.

Methods of treatment

The present invention also encompasses methods for treatment of progestogen-responsive syndromes, such as, for example, in hormone replacement therapy. Also encompassed are other modes of progestogen administration such as, for example, for contraception and treatment of osteoporosis. The methods are carried out by administering the formulation described above to a subject in need of a progestogen (or, a combination of a progestogen and another active ingredient, such as, for example, an estrogen). Progestogen-responsive syndromes include, without limitation, infertility related to non-receptive uterus, premenstrual tension, ovulation, primary dysmenorrhea and endometriosis, habitual abortion, respiratory depression in the Pickwickian syndrome, secondary amenorrhea, dysfunctional uterine bleeding, preeclampsia and toxemia of pregnancy, sexual infantilism, and post-menopausal symptoms.

The formulation of this invention is administered in a manner known per se, for example according to the instructions given by a doctor. A convenient way of administration is via the oral route (per orally).

All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference in their entirety and to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein (to the maximum extent permitted by law).

The mentioning herein of a reference is no admission that it constitutes prior art.

All headings and sub-headings are used herein for convenience only and should not be construed as limiting the invention in any way.

Herein the word "comprise" is to be interpreted broadly meaning "include", "contain" or "comprehend" (vide, for example, Guidelines for Examination in the European Patent Office, Part C, Chapter III, 4.13).

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The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

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The citation and incorporation of patent documents herein is done for convenience only and does not reflect any view of the validity, patentability, and/or enforceability of such patent documents.

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This invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law.

Example 1: Enhanced stability of NETA in a low-dose formulation

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The purpose of this study was to compare the effect of (i) different binders and (ii) different coatings on stability of NETA in a low-dose formulation.

Table II below illustrates the test formulations:

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Table II

Ingredients	Quantity (mg/tablet)	Function	Commercial Source
Active Ingredients			
Estradiol hemihydrate	0.517	Active substance	Schering AG, Germany / Diosynth B.V., Holland
Norethisterone Acetate	0.100	Active substance	Schering/Diosynth
Other ingredients			

Lactose monohydrate	37.5	Filler	DMV International, Holland
Maize starch	37.5	Disintegrant / filler	Cerestar Scandinavia
Binder	3.20	Binder	
Talc	0.800	Glidant / lubricant	Luzenac, Italy
Magnesium stearate	0.400	Lubricant	Acros Chemicals

Two different binders were tested: Polyvidon™ VA 64 (polyvinylpyrrolidone, BASF, Germany); and Klucel™ EF Pharm (hydroxypropyl cellulose, Aqualon, USA).

5 Tabletting and coating: Tablets containing the two binders were formed by fluid-bed granulation, compression on rotary press, film-coating in a coating pan using an air atomizing spray system. For film coating, either 1% or 3% Methocel E3 was used. The final tablets contained the film-coat components mentioned in tables III and IV, below:

Table III

10

1% film coat:

Film-coating: (theoretical quantity mg/tablet)	0.864
Filmformer	0.821
Glycerol triacetate	0.043

Table IV

15 3% film coat:

Film-coating: (theoretical quantity mg/tablet)	2.400
Filmformer	2.280
Glycerol triacetate	0.120

Packaging: Following coating, each tablet batch was packed in a calendar dial pack ("Dispenser").

20 Stability testing: The packaged products were stored at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ / 75% relative humidity (hereinafter designated RH) $\pm 5\%$ RH for 6 months. The products were subjected to assay analysis during the 6-months period. Statistically analysis was based upon analysis after 0, 3, and 6 months. At 6 months after initiation of the study, products were subjected to

assay analysis using HPLC to detect NETA and estradiol.

Results:

- A statistical evaluation of up to 6-month assay data from storage condition 40°C/75 %RH was performed. Differences in formulations were evaluated by comparing the degradation rates (slopes) of NETA. NETA degradation was found to be dependent on both binder and film-coat amount. The type of film former (Methocel E3 or E5) did not significantly affect degradation.
- The time in months until a significant change (5 %) at 40°C/75%RH (Ref. ICH Q1 A(R2) 'Stability Testing of New Drug Substances and Products') of NETA assay occurred was calculated based on the degradation rates.
- Estimates of the equivalent degradation rates at 25°C were calculated using the Arrhenius equation in accordance with the principle in 'Chemical Stability of Pharmaceuticals. A Handbook for Pharmacists' Connor, K.A., Amidon, G. L. and Kennon, L. John Wiley & Sons, New York, 1978. The degradation rates were then used to calculate the time in months until a significant change of NETA occurred at 25°C.
- The results are given in table V below:

Table V

Film-coat amount, %	Binder	The time (months) until a significant (5 % label claim) change in assay NETA occurs	
		40°C	25°C
1	Klucel EF	3.5	18.3
	Polyvidon VA64	3.2	16.6
3	Klucel EF	5.0	25.9
	Polyvidon VA64	3.9	20.4

The results demonstrate that Klucel EF is superior to Polyvidon in enhancing NETA stability and that 3% film coat is superior to 1 %.

5 The results demonstrate that (i) cellulosic binders are superior to polyvidon in enhancing NETA stability and (ii) a 3% Methocel coat is superior to a 1% coat in enhancing NETA stability.

The disintegration time of the tablets, tested according to the European Pharmacopoeia 4th edition 2002, item 2.9.1. test A, was less than 10 minutes.

CLAIMS

1. A pharmaceutical formulation comprising (i) a progestogen and (ii) a cellulosic binder, having a content of NETA in the range from 0.05 to 1.5% (w/w) relative to the total formulation or an equivalent amount of a non-NETA progestogen.
5
2. The formulation according to claim 1, wherein the content of said progestogen is not more than about 1.3% (w/w) relative to the composition.
- 10 3. The formulation according to the preceding claim, wherein the content of said progestogen is not more than about 0.75% (w/w).
4. The formulation according to the preceding claim, wherein the content of said progestogen is not more than about 0.5% (w/w).
15
5. The formulation according to the preceding claim, wherein the content of said progestogen is not more than about 0.25% (w/w).
6. The formulation according to the preceding claim, wherein the content of said progestogen is not more than about 0.1% (w/w).
20
7. A pharmaceutical formulation comprising (i) a progestogen and (ii) a cellulosic binder, said formulation containing NETA in the range from 0.05 to 1.3 mg or containing an equivalent amount of a non-NETA progestogen per unit dosage form.
25
8. The formulation according to any one of the preceding claims, wherein the stability of said progestogen in said formulation is enhanced relative to the stability of progestogen in an identical formulation which deviates only in that the cellulosic binder has been exchanged by an identical amount of polyvinylpyrrolidone and, said enhancement is preferably at
30 least 5%, more preferred at least 10 %, even more preferred at least 15%.
9. The formulation according to any one of the preceding claims, wherein said cellulosic binder is selected from the group consisting of methylcellulose, sodium carboxymethylcellulose, preferably Tylose™, ethylcellulose, preferably Ethocel™, hydroxypropyl methyl
35 cellulose (herein designated HPMC), and hydroxypropyl cellulose, preferably Klucel™.

10. The formulation according to any one of the preceding claims, wherein the content of cellulosic binder is in the range from 2 to 10% (w/w) relative to the total composition.

11. The formulation according to any one of the preceding claims, wherein said cellulosic binder is hydroxypropyl cellulose, preferably Klucel™.

12. The formulation according to any one of the preceding claims wherein said cellulosic binder is hydroxypropyl cellulose having a molecular weight in the range from 30,000 to 1,500,000, preferably in the range from 50,000 to 150,000.

13. The formulation according to any one of the preceding claims, wherein said cellulosic binder is hydroxypropyl cellulose, preferably hydroxypropyl cellulose fulfilling the requirements of European Pharmacopoeia and the United States National Formulary.

14. The formulation according to any one of the preceding claims, wherein said progestogen is selected from the group consisting of medroxyprogesterone acetate, chlormadinone acetate, megestrol acetate, cyproterone acetate, norethindrone, norethynodrel, lynestrenol, norethindrone acetate (herein designated NETA), ethynodiol acetate, and norethindrone enanthate, norgestrel (-d or -l), norgestimate, desogestrel, gestodene, osaterone, dienogest, chlormadinone acetate, and drospirenone.

15. The formulation according to any one of the preceding claims, wherein said progestogen is a 19-nortestosterone derivative, preferably norgestrel, laevonorgestrel, NET or NETA.

16. The formulation according to any one of the preceding claims, wherein said progestogen is a soluble ester or salt of norethindrone, preferably a soluble ester, more preferred NETA or norethindrone enanthate.

17. The formulation according to the preceding claim, wherein said progestogen is NETA.

18. The formulation according to the preceding claim, wherein the content of NETA is in the range from 0.07 to 1.3 mg per unit dosage.

19. The formulation according to the preceding claim but one, wherein the content of NETA is in the range from 0.1 to 0.35 mg per unit dosage.

20. The formulation according to the preceding claim but two, wherein the content of NETA is in the range from 0.3 to 0.7 mg per unit dosage.
- 5 21. The formulation according to the preceding claim but three, wherein the content of NETA is in the range from 0.7 to 1.3 mg per unit dosage.
22. The formulation according to any one of the preceding claims, containing an oestrogen.
- 10 23. The formulation according to the preceding claim, wherein said estrogen is estradiol, optionally as a hydrate such as the hemihydrate.
24. The formulation according to the preceding claim, wherein the content of estradiol hemihydrate is in the range from 0.3 to 2.5 mg per unit dosage.
- 15 25. The formulation according to the preceding claim, wherein the content of estradiol hemihydrate is in the range from 0.3 to 0.7 mg per unit dosage.
26. The formulation according to the preceding claim but one, wherein the content of estradiol hemihydrate is in the range from 0.7 to 1.3 mg per unit dosage.
- 20 27. The formulation according to the preceding claim but two, wherein the content of estradiol hemihydrate is in the range from 1.7 to 2.3 mg per unit dosage.
28. The formulation according to any one of the preceding claims, containing lactose in an amount in the range from 30 to 45 mg, optionally as lactose monohydrate.
- 25 29. The formulation according to any one of the preceding claims, containing maize starch in an amount in the range from 30 to 45 mg.
- 30 30. The formulation according to any one of the preceding claims, containing hydroxypropyl-cellulose in an amount in the range from 2 to 10 mg.
31. The formulation according to any one of the preceding claims, containing talc in an amount in the range from 0.5 to 2 mg.
- 35

32. The formulation according to any one of the preceding claims, containing magnesium stearate in an amount in the range from 0.1 to 1 mg.

33. The formulation according to any one of the preceding claims, containing hydroxypropylmethyl cellulose as film coater in an amount in the range from 0.5 to 3 mg.

34. The formulation according to any one of the preceding claims, containing glycerol triacetate in an amount in the range from 0.05 to 0.2 mg.

35. The formulation according to any one of the preceding claims, comprising an amount in the range from 0.2 to 1 mg of estradiol hemihydrate, an amount in the range from 0.05 to 0.5 mg of NETA, and an amount in the range from 2.5 to 4 mg of a cellulosic binder, wherein said cellulosic binder is selected from the group consisting of methylcellulose, sodium carboxymethylcellulose, ethylcellulose, hydroxypropyl methyl cellulose, and hydroxypropyl cellulose.

36. The formulation according to any one of the preceding claims, comprising about 0.5 mg of estradiol hemihydrate, about 0.1 mg NETA, about 40 mg of lactose monohydrate, about 40 mg of maize starch, about 3 mg of hydroxypropyl cellulose or hydroxypropyl methyl cellulose, about 0.8 mg of talc, and about 0.4 mg of magnesium stearate.

37. The formulation according to any one of the preceding claims, further comprising a cellulosic coating.

38. The formulation according to any one of the preceding claims, wherein said cellulosic coating is selected from the group consisting of methylcellulose, sodium carboxymethylcellulose, preferably Tylose™, ethylcellulose, preferably Ethocel™, hydroxypropyl methyl cellulose (herein designated HPMC), and hydroxypropyl cellulose, preferably Klucel™.

39. The formulation according to any one of the preceding claims, wherein said cellulosic coating is hydroxypropyl methyl cellulose.

40. The formulation according to any one of the preceding claims, wherein said coating is present in an amount in the range from 0.5 to 5% (w/w) relative to the total formulation.

41. The formulation according to the preceding claim, wherein said coating is present in an amount in the range from 2 to 4% (w/w) relative to the total formulation.
- 5 42. The formulation according to any one of the preceding claims, wherein said coating is present in an amount in the range from 2.5 to 3.5% (w/w) relative to the total formulation.
43. The formulation according to any one of the preceding claims, wherein the total amount of said coating is in the range from 2 to 3 mg per unit dosage.
- 10 44. The formulation according to any one of the preceding claims, which is a pellet, tablet or capsule.
45. The formulation according to any one of the preceding claims, which has a loss of mass (w/w) of not more than 15%, preferably of not more than 10 %, when tested according to
15 European Pharmacopoeia 4th edition 2002, item 2.2.32, test C.
46. The formulation according to any one of the preceding claims, which by the method described in European Pharmacopoeia 4th edition 2002, item 2.9.1, test A, disintegrates within 2 hours, preferably 1 hour, more preferred 30 minutes, most preferred 15 minutes.
20
47. A method for stabilizing a progestogen component of a pharmaceutical formulation, said method comprising contacting said progestogen with a stabilizing-effective amount of a cellulosic binder, wherein said progestogen is present in an such an amount that the content of said progestogen is in the range from 0.05 to 1.5% (w/w) relative to the total
25 weight of the formulation.
48. The use of the pharmaceutical formulation as claimed in any one of claims 1 to 46 in a method of manufacturing a medicament for use in the treatment of a progestogen-responsive syndrome comprising administering an effective amount of said formulation to
30 a patient in need of such treatment.