Product Monograph

dydrogesterone
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Introduction
Introduction

Duphaston (dydrogesterone) was first introduced to the market in 1961, and is currently approved in over 100 countries world-wide. It has an estimated cumulative exposure of more than 28 million patients.

Duphaston is a potent, orally active progestogen indicated in a wide variety of gynaecological conditions. Although similar in molecular structure and pharmacological effects to endogenous progesterone, Duphaston is orally active at far lower doses. Its freedom from oestrogenic, androgenic, anabolic, corticoid and other undesirable hormonal effects gives it additional benefits over most other synthetic progestogens.

The therapeutic use of Duphaston is closely related to its physiological action on the neuro-endocrine control of ovarian function, as well as on the endometrium. As such, Duphaston is indicated in all cases of relative or absolute endogenous progesterone deficiency.

Duphaston has proven effective in the following conditions:
- menstrual disorders
- infertility
- threatened and habitual abortion
- endometriosis
- premenstrual syndrome

Duphaston has also been registered as hormone replacement therapy (HRT) to counteract the negative effects of unopposed oestrogen on the endometrium. Duphaston is safe and well-tolerated. The incidence of side-effects is remarkably low.

Duphaston® in Menstrual Disorders

Dysmenorrhoea
Primary or essential dysmenorrhoea is one of the most common gynaecological complaints of women during their reproductive years. Duphaston relieves the pain associated with incapacitating dysmenorrhoea, decreases the need for analgesics and reduces absenteeism from work.

Secondary amenorrhoea
Secondary amenorrhoea is a symptom rather than a specific disease. Duphaston adequately induces bleeding when the endometrium is sufficiently primed with oestrogens. When oestradiol levels are low, Duphaston treatment should be supplemented with oestrogens.

Dysfunctional uterine bleeding and irregular cycles
Of the wide range of medications used to reduce heavy menstrual bleeding in patients with ovulatory cycles, oral progestogens like Duphaston are the most commonly prescribed. Duphaston prevents heavy bleeding.

Duphaston® in Infertility and Threatened and Habitual Abortion

Luteal insufficiency
Luteal insufficiency leads to inadequate ovarian progesterone production, which in turn results in an incomplete secretory endometrium and ineffective ovum implantation. Duphaston almost doubles pregnancy rates compared to placebo.

Threatened and habitual abortion
The incidence of spontaneous abortion is about 15% of all clinically recognised pregnancies. Progestogens are commonly used in threatened and habitual abortion. They are thought to exert their effect in two ways. Firstly, by restoring luteal function, thereby decreasing the incidence of first trimester abortions. Secondly, through relaxation of the smooth musculature of the uterus.

More recently, the evidence indicates that modulation of the maternal immune response during early pregnancy also contributes to the anti-abortive effects of Duphaston. In clinical practice, Duphaston achieved success rates of 70% or higher.

Duphaston is recommended in the treatment of infertility for several reasons:
- it has no inhibitory effect on ovulation
- it does not alter the normal pattern of secretory transformation of the endometrium
- it does not inhibit the formation of progesterone in the human placenta during early pregnancy
- it does not cause masculinisation of the female foetus.
**Duphaston® in Endometriosis**

Endometriosis is a chronic disease which can cause severe, progressive, and at times, incapacitating dysmenorrhoea, pelvic pain, dyspareunia and infertility. Duphaston relieves pain without inhibiting ovulation, so that patients are able to become pregnant during treatment. The efficacy of Duphaston on the lesions of endometriosis is less clear, but their number and severity does not seem to correlate with the severity of symptoms.

**Duphaston® in Premenstrual Syndrome**

Premenstrual syndrome (PMS) is characterised by a range of mood swings and physical symptoms. Duphaston effectively relieves a number of these and is especially indicated when:
• PMS is associated with hypermenorrhoea and dysmenorrhoea
• other treatments such as oral contraceptives for ovulation suppression, or psychotropic medication are contraindicated.

**Duphaston® in Hormone Replacement Therapy (HRT)**

The principle behind HRT is two-fold:
• to actively increase the circulating levels of oestrogens to control hot flushes
• to prevent the long-term effects of the menopause, such as bone resorption and unfavourable changes in blood lipids.

The administration of 17β-oestradiol halts, or reverses atrophic changes that occur due to the loss of endogenous oestradiol during the menopause.

Oestrogens stimulate the growth of endometrial cells. In postmenopausal women with an intact uterus, oestrogen monotherapy results in continued endometrial proliferation without the physiological secretory transformation normally induced by progesterone. This process is associated with an increased incidence of endometrial hyperplasia and carcinoma. Additional protection with progestogens is therefore mandatory in patients with an intact uterus who receive oestrogen replacement therapy.

Duphaston opposes the proliferative effect of oestrogens on the endometrium and ensures conversion to a secretory pattern and cyclical shedding of the endometrium in sequential HRT regimens. As such Duphaston effectively guards against the development of endometrial hyperplasia.

Unlike androgenic progestogens, Duphaston does not reverse the beneficial effects of 17β-oestradiol on lipid profiles and carbohydrate metabolism. This makes it a progestogen of choice, as illustrated by its excellent cycle control in sequentially combined HRT. In a continuous combined HRT regimen, Duphaston inhibits the proliferation of the endometrium so that it remains atrophic or inactive. The majority of patients become amenorrhoeic after 6 months of treatment.
Duphaston®: Chemistry, Pharmacokinetics, Pharmacology and Toxicology

Chemistry
Duphaston (9ß, 10α-pregna-4, 6-diene-3, 20-dione) was first synthesised by Duphar in the 1950s. Although its molecular structure is almost identical to that of natural progesterone, its unique design makes it a potent, orally active progestagen. In the dydrogesterone molecule, the hydrogen atom at carbon 9 is in the beta position and the methyl group at carbon 10 is in the alpha position - a reverse of the progesterone structure, hence the term ‘retro’ progesterone. Furthermore, Duphaston has a second double-bond between carbon 6 and carbon 7 (the 4, 6-diene-3-one configuration). These small differences in chemical structure account for the improved oral activity, metabolic stability, and the lack of oestrogenic, androgenic and mineralo-corticoid properties of Duphaston.

Pharmacokinetcs
Duphaston is readily absorbed after oral administration. T\textsubscript{max} values vary between 0.5 and 2.5 hours.\textsuperscript{1}

Metabolisation of Duphaston is virtually complete. The main metabolic reaction is hydrogenation of the 20-keto group, resulting in 20-dihydrodydrogesterone (DHD), another potent progestagen. The levels of the main active metabolite DHD also peak about 1.5 hours after dosing.\textsuperscript{1}

After oral administration, plasma concentrations of DHD are substantially higher than those of the parent drug. The ratios of DHD/Duphaston for AUC and C\textsubscript{max} are in the order of 40 and 25, respectively. Absolute bio-availability is on average 28%.\textsuperscript{1}

Duphaston. Specifically designed ‘retro’ steroid
• Better oral activity and metabolic stability
• Highly selective for the progesterone receptor - lack of androgenic and oestrogenic effects

Duphaston. A metabolism devoid of adverse effects
• Metabolites retain the 4, 6-diene-3-one structure and are metabolically stable
• No aromatisation, consistent with its absence of oestrogenic effects
• No 17α-hydroxylation, explain its lack of androgenic effects

Duphaston. Does not compromise the benefits of oestrogen

Pharmacology
Duphaston has superior pharmacological properties compared to endogenous progesterone:
• It is orally active at low dosages
• It has selective progestogenic properties without any additional hormonal activity.
Duphaston is characterised by progestational and anti-oestrogenic activity. This is demonstrated by its ability to induce a secretory transformation in the endometrium of immature or ovariectomised animals after they have been primed with oestrogens (cf. the Clauberg test). The oral progestogenic potency of Duphaston is 20 times higher than that of progesterone.\(^3,4\)

The progestational efficacy and potency of Duphaston was confirmed by standard tests (i.e. delay of menses and induction of withdrawal bleeding).\(^5\)

The benefits of oestrogen on other target organs are not compromised by Duphaston.

**Figure 3**

Duphaston effectively induces endometrial transformation in menopausal women\(^6\)

- **Global morphological score**
  - 0
  - 20
  - 40
  - 60
  - 80
  - 100
  - 120

Without progesterone
- Norethindrone
- Dienogest
- Medroxyprogesterone acetate
- Duphaston
- Progesterone

Morphological transformation of the endometrium induced by different doses of progestogens. The overall morphological score is the sum of the scores obtained for the individual histological parameters.

Unlike other synthetic progestogens, Duphaston is not chemically related to testosterone. Its low affinity for the androgen receptor explains why it has no unwanted androgenic or anti-androgenic effects even at high doses and after prolonged treatment:\(^1,7-15\)
- no virilisation (acne, voice changes, hirsutism) of the adult female
- no virilising effects on the genital tract of the female foetus
- no effect on the fertility of the offspring.

Duphaston is not converted into oestrogen, and has no adverse oestrogenic effects on fertility or sexual development.\(^16-18\)

At recommended doses, Duphaston has no effect on ovulation in healthy women.\(^19-21\)
- the biphasic pattern of the basal body temperature is maintained
- normal ovulatory rise in oestrogen and pregnanediol
- normal premenstrual biopsy
- no modification of vaginal cytology
- cytological evidence of ovulation
- the formation of the corpus luteum has been confirmed by laparotomy.

These beneficial results are of particular relevance to the use of Duphaston in women who wish to become pregnant.

Duphaston is free from adverse effects on carbohydrate metabolism. It does not cause changes in body weight,\(^22\) blood pressure, glucose tolerance or blood lipid ratios. No significant effects on blood coagulation or liver function tests have been reported.\(^23,24\) These favourable results are crucial in long-term therapy, e.g. postmenopausal HRT.

**Duphaston®.**

**Superior pharmacological properties**
- orally active at low dosages
- selective progestogenic properties without any additional hormonal activity
- progestational and anti-oestrogenic activity as demonstrated by its ability to induce a secretory transformation in the endometrium
- oral progestogenic potency 20 times higher than progesterone
- does not compromise beneficial actions of oestrogen on other target organs
- low affinity for the androgen receptor explains why it has no unwanted androgenic or anti-androgenic effects even at high doses and after prolonged treatment, and no effect on the fertility of the offspring
- at recommended doses, no effect on ovulation
- free from adverse effects on carbohydrate metabolism, does not cause changes in body weight, blood pressure, glucose tolerance or blood lipid ratios. No significant effects on blood coagulation or liver function tests have been reported.

**Toxicology**

No serious or unexpected toxicity has been observed with Duphaston. In acute toxicity studies, the LD\(_{50}\) doses in rats exceeded 4,840mg/kg for the oral route.

There was no evidence of mutagenic potential in the Ames test.
Clinical Experience with Duphaston®
Clinical Experience with Duphaston®

In non-pregnant women, progesterone is synthesised primarily by the ovaries and by the adrenal cortex. During the menstrual cycle, the corpus luteum produces progesterone, and serum concentrations of 3 to 25 ng/ml are attained. A small fraction of progesterone remains free in the plasma whilst the remainder is bound to albumin and, to a lesser extent, corticosteroid-binding globulin.

The majority of progesterone effects, including those on ovulation and implantation, occur as a result of receptor-mediated action, although some non-receptor-mediated effects have also been demonstrated. Progesterone receptors are widely distributed in the body, including the uterus (mammalian endometrium and myometrium) and the ovaries (luteinising granulosa cells and corpus luteum and pre-ovulatory granulosa cells). Specific progestogen binding has been observed in other reproductive tissues as well as in others where its actions are less well defined. In most target tissues, the expression of progesterone receptors is up-regulated by oestrogen and down-regulated by progesterone.

Duphaston has pharmacological effects similar to endogenous progesterone, and is indicated in all cases of relative or absolute endogenous progesterone deficiency. It has proved effective in the treatment of menstrual disorders, infertility due to luteal insufficiency, threatened and habitual abortion, endometriosis and premenstrual syndrome.

The results from earlier studies on the use of Duphaston in these indications are not discussed in detail here.

Duphaston® in Menstrual Disorders

Dysmenorrhoea

Dysmenorrhoea (‘painful menstruation’) is characterised by pelvic pain and other disturbances occurring just before, or during the menstrual period. The pain is usually sharp, cramping and intermittent in nature, localised at the waist-line and the lower abdomen, but sometimes extending to the vagina, lower back or thighs. Accompanying symptoms include nausea, vomiting, headache, backache, nervousness, irritability and joint pain.

Primary (or essential) dysmenorrhoea is one of the most common gynaecological complaints of the reproductive years, in particular in adolescence. Pelvic pain is caused by the contraction of the myometrium and increased concentration of prostaglandins in the endometrium. Duphaston brings welcome relief to this condition.

Duphaston is thought to exert its beneficial effects through a decrease in the rate of prostaglandin synthesis, since this rate has been shown to be inversely proportional to levels of progesterone. The oestrogen/progesterone ratio in the myometrium may also play a part, since the luteal hormone has been shown to have an anti-tetanic effect, thereby permitting the uterine muscle to relax between contractions.

Bishop (1961), was the first to report that Duphaston relieved the pain of incapacitating dysmenorrhoea without inhibiting ovulation. The overall success rate was 83%, and no unpleasant side-effects were reported. The results from five studies reported between 1965 and 1985 (four double-blind, and one single-blind) confirmed his findings.

More recently, Ohlenrothe and Hatzmann recorded a total of 437 cycles of Duphaston in 67 young patients (mean age 16.8 years) with primary dysmenorrhoea. Only five patients did not obtain a positive response. Of the remaining 62, 33 were asymptomatic after the first cycle, and the dysmenorrhoea regressed markedly in the rest.

Clinical Experience with Duphaston®

Dysmenorrhoea

100% reduction in symptoms

7% improvement

49% without response

81% without symptoms after 1 cycle

93% with positive response

Figure 4

Duphaston effectively relieves symptoms in the majority of women with juvenile dysmenorrhoea.
The Battino study was double-blind, reference-controlled, and showed similar response rates for Duphaston and medroxyprogesterone acetate.

The success of Duphaston® in secondary amenorrhoea depends on whether the endometrium has been sufficiently primed with oestrogens (either exogenous or endogenous). The Battino study was double-blind, reference-controlled, and showed similar response rates for Duphaston and medroxyprogesterone acetate.

**Secondary Amenorrhoea**

Secondary amenorrhoea occurs when regular menstruation ceases for at least 6 months in the absence of pregnancy, lactation or a normal menopause. It can also refer to amenorrhoea that lasts 50 days or more (oligomenorrhoea). Secondary amenorrhoea is a symptom, not a specific disease. Its causes can be anatomical/pathological, endocrine or iatrogenic in nature.

The administration of a progestogen can be used as a diagnostic tool to discover whether or not the endometrium is responsive and sufficient endogenous oestrogen is being produced. Sufficient endogenous oestrogen but a lack of progestogen is most typical for all forms of luteal insufficiency, e.g. due to anovulatory cycles in menarche or menopause, or in women with polycystic ovaries.

The power of Duphaston to induce withdrawal bleedings has been demonstrated extensively. The overall success rate in the controlled studies, with relatively large patient samples, ranged between 73% and 92%. Results from smaller patient samples tended to be somewhat higher, with success rates between 97% and 100%. More recently, Serfaty et al, Nakamura et al, and Battino et al reported response rates of 90% and higher. Serfaty evaluated the efficacy of Duphaston in women with residual oestrogen secretion (positive test: withdrawal bleeding after 10 days of dydrogesterone), as well as in women with severe lack of oestrogen (negative test: withdrawal of dydrogesterone did not induce bleeding). The latter women were treated with Duphaston in combination with an oestrogen. Success rates were 92% and 90.5% respectively.

Fairweather reported that Duphaston treatment relieved pain in 60% of patients, compared to 30% with placebo. Consequently, absence from work through sickness occurred in only 35% following Duphaston, and in 70% receiving placebo. Analgesics were never required during Duphaston treatment, only with placebo. Results from other studies have confirmed that patients treated with Duphaston use significantly fewer analgesics.

**Duphaston® is therefore a highly suitable treatment for relief of dysmenorrhoea. It decreases the incidence and severity of complaints, the need for analgesics and the number of days absent from work.**

**Duaphlaston. Effective in secondary amenorrhoea**

10mg twice daily from day 11 to 25 of the cycle

- When amenorrhoea results from a deficient luteal phase in patients with normal or high oestradiol levels, Duphaston (14 days in each cycle) could protect the endometrium

Patients with normal or high oestradiol levels and amenorrhoea resulting from a deficient luteal phase, have been reported to be at increased risk from endometrial hyperplasia and carcinoma. In these patients, Duphaston (14 days in each cycle) could protect the endometrium against unopposed oestrogens. The ability of Duphaston to induce withdrawal bleeding in an endometrium that is sufficiently primed with oestrogens has recently been extensively confirmed in publications on HRT in postmenopausal women (see page 35).
**Dysfunctional Uterine Bleeding and Irregular Cycles**

Dysfunctional uterine bleeding (DUB) is defined as excessively heavy, prolonged or frequent bleeding which is not due to recognisable pelvic or systemic disease. It is a common condition affecting about 20% of women. Menorrhagia is generally defined as a loss of more than 80ml of menstrual blood (compared to an average menstrual blood loss of 35-45ml). In practice, diagnosis is based on a history of menstrual flooding, loss of large blood clots, and social disability related to menstrual bleeding. DUB is poorly tolerated by the majority of women who suffer from it.

Most women with DUB have regular ovulatory cycles. But sometimes the bleeding is associated with anovulation, especially when it arises at the beginning and end of reproductive life. In anovulatory DUB, irregular cycles result from irregular oestrogen production without secretory transformation and progestogen withdrawal. Prolonged oestrogen stimulation may cause endometrial hyperplasia and erratic bleeding resulting from its break-down and expulsion. In women with anovulatory cycles, Duphaston, used during the second half of the menstrual cycle (with or without additional administration of oestrogens during the first half of the cycle), provokes regular withdrawal bleeding.55

The clinical relevance of progestogens in situations of abnormal bleeding, and the cellular and molecular mechanisms underlying it, have recently been reviewed.56 Of the wide variety of medications used to reduce heavy menstrual bleeding in women with anovulatory cycles, oral progestogens are the treatments most commonly prescribed.57-60 The beneficial effect of Duphaston results from a restoration of the balance of prostaglandins PGF2 and PGE2 in the endometrium, which is disturbed in menorrhagic women.56,61

A large number of baseline-controlled studies dating back to the 1960s and early 1970s have been reported in the literature. The overall mean success rate of Duphaston exceeded 80%.

**Figure 6**

Duphaston effectively reduces the length of the menstrual cycle33

More recently, Tabaste reported that 10mg Duphaston twice daily on days 16 to 25 of each cycle reduced the mean length of the cycle from 40 to 28 days, and the length of the menstrual bleeding from 6 to 5 days. Symptoms of dysmenorrhae were resolved in 75% of all patients.33

In two recently reported trials in adolescent patients with cycle disturbances and DUB, Duphaston arrested bleeding in all but one patient, and regulated menstrual cycle in all patients.62,63

*These data confirm the efficacy and safety of Duphaston™ in the treatment of DUB.*
Most of the trials that were included in the reviews of Karamardian and Grimes\textsuperscript{71} and of Soliman et al\textsuperscript{72} investigated the effect of progestogen supplementation as a prophylactic agent in assisted reproduction programmes, e.g., during an insemination cycle, or following in vitro fertilisation (IVF). Only a few studies have assessed the effectiveness of progestogen supplementation outside of IVF.

One trial compared the use of Duphaston versus progesterone and placebo in 44 infertile women with histologically proven LPD.\textsuperscript{75} Patients were either treated with oral Duphaston 20mg/day (n=16) or progesterone 25mg suppositories twice daily (n=16). Treatment started 3 days after a rise in basal body temperature. A third control group of 12 patients received no treatment at all. Treatment success was defined as correction of the endometrial defect during the fourth treated cycle, or when a term pregnancy was achieved. The success rate in the Duphaston group was 69%, compared to 63% in the progesterone group (p<0.001), and 17% in the control group (p<0.001). Pregnancy rates were 31% in both active treatment groups, and 17% in the placebo group. Though the trial was not sufficiently powered to detect differences in pregnancy rates\textsuperscript{71} the authors concluded that both Duphaston and progesterone are effective in the treatment of LPD.

Duphaston\textsuperscript{®} has the advantage, however, in that it does not alter the normal pattern of secretory transformation of the endometrium.\textsuperscript{17}

**Figure 7**

 Oral Duphaston is at least as effective as intra-vaginal progesterone in the treatment of luteal phase deficiency.\textsuperscript{75}

\[\text{Success rate (\%)}\]

- **Controls**
- **Progesterone suppositories 25mg bid**
- **Duphaston 20mg od**

- \*p<0.001
- \#p=0.001

\[\text{Normal secretory pattern confirmed by biopsy in the fourth treated cycle, or term pregnancy}\]

**Duphaston in Infertility and in Threatened and Habitual Abortion**

**Due to Luteal Phase Deficiency**

Luteal insufficiency is the most serious consequence of a dysfunctional corpus luteum and results in inadequate ovarian progesterone production. Lack of progesterone causes an incomplete secretory endometrium and consequently ineffective ovum implantation.

In 1949, Jones showed that infertile women had lower plasma progesterone levels than fertile women\textsuperscript{64} and proposed luteal phase deficiency (LPD) as a cause. The prevalence of LPD as a cause of infertility is estimated to be somewhere between 3.5% and 20%. Little agreement exists over diagnostic criteria or the aetiology, pathophysiology or response to treatment. Diagnostic methods include endometrial biopsies, luteal phase duration, basal body temperature charts, serum progesterone measurements, ultra-sonographic determination of follicle size and serum prolactin measurements. A serum progesterone level of <21nmol/l was proposed as the optimal discriminatory level between LPD and normal cycles.\textsuperscript{65}

The most common treatment for LPD is progestogen supplementation. Oral progesterone has shown itself to be more effective than vaginal. Vaginal supplementation might directly stimulate endometrial production of insulin-like growth factor-binding protein-1 (IGFBP-1), which possibly determs embryo implantation.\textsuperscript{66} Oral forms are also more convenient and better tolerated.\textsuperscript{66-69} Other treatments include clomiphene citrate, FSH, bromocriptine and hCG, though few studies have appropriately evaluated their effectiveness.

**Duphaston\textsuperscript{®} is particularly useful in infertility due to LPD because:**\textsuperscript{70}

- It has no inhibitory effect on ovulation
- It does not inhibit the formation of progesterone in human placenta during early pregnancy
- It does not cause masculinisation of the female foetus.

Two reviews published in the past decade discussed the effect of progestogen treatment on pregnancy rates in LPD.\textsuperscript{71,72} The conclusions drawn by Karamardian and Grimes\textsuperscript{71} were largely negative, stating that “there is insufficient evidence to make recommendations concerning treatment of luteal phase support”. This negative outcome was due to inadequate methodology, however, as well as poor reporting and a lack of power in the studies that the authors reviewed. The conclusions of Soliman et al\textsuperscript{72}, on the other hand, were more positive. They performed a meta-analysis of randomised trials, including two trials with Duphaston\textsuperscript{73,74} and concluded that the pregnancy rate was significantly higher in the patient groups who were treated with progestogens.

\[\text{Recommended in infertility due to luteal insufficiency}\]

10mg twice daily from day 14 to 25 of the cycle - treatment should be maintained for at least 6 consecutive cycles - it is advisable to continue treatment for the first few months of pregnancy as described in habitual abortion

- Little impact on physiological processes other than its direct effect on the progesterone-receptor
Two other studies with Duphaston were baseline-controlled. Vanrell and Balasch treated 21 patients with endometrial progesterone insufficiency either with oral Duphaston (10mg/day, n=10) or progesterone suppositories (25mg twice daily, n=11). Treatment was initiated from the third day after a rise in basal body temperature and continued for 10 days. A total of 57% (n=12) of patients became pregnant, 19% of whom (n=4) aborted. The risk of abortion was smaller with Duphaston (10%, n=1), than with progesterone (27%, n=3).

Taubert studied 46 patients suffering from infertility. Luteal phase deficiency was diagnosed by abnormal body temperature charts and histological examination of the endometrium. A total of 41 patients were treated with Duphaston alone (5-10mg/day from day 17 to 26 of each cycle), whilst five patients were given a combination treatment consisting of Duphaston 10mg/day and 0.02mg ethinyloestradiol. Thirteen patients treated with Duphaston alone conceived. But there were only two pregnancies with combination therapy. The overall success rate of Duphaston was therefore 33%. Patients in this study were classified as having either absolute, relative or suspected LPD, and the authors commented that the diagnostic criteria were weak, with the implication that the Duphaston scores could have been significantly higher.

Because Duphaston is well-tolerated and its action focused on the progesterone receptor, its use is recommended where infertility due to luteal insufficiency is suspected.

Threatened and Habitual Abortion

Threatened abortion is the most frequent pathology of pregnancy with an estimated incidence of 15 to 20%. Habitual abortion is defined as a sequence of three or more consecutive abortions. Spontaneous abortion constitutes about 15% of all clinically recognised pregnancies. The majority (50-60%) of all pregnancy losses are due to structural chromosomal abnormalities of the foetus, but other factors e.g. hormonal or immunogenetic have also been suggested to explain the loss. The prevalence of LPD in women with recurrent abortions lies somewhere between 23% and 60%.

Progestogens are commonly used in threatened and habitual abortion. They restore luteal insufficiency, thereby decreasing the incidence of first trimester abortions. Progestogens also have a general relaxing effect on the smooth musculature of the uterus, a state that is considered beneficial throughout pregnancy.

Recent data have pointed out that the anti-abortive effects of progesterone during early pregnancy may arise through modulation of the maternal immune response. In the presence of progesterone, activated lymphocytes synthesise a 34kDa protein: progesterone induced blocking factor (PIBF).

PIBF prevents inflammatory and thrombotic secondary reactions towards the trophoblast through three distinct actions:

- by inducing asymmetric, protective ‘blocking’ antibodies
- by blocking natural killer (NK) cell degranulation
- by inducing T-helper 2 (Th2) cell dependent cytokines, thereby shifting the balance towards a Th2-dominated, cyto-protective immune response.
Habitual abortion

Studies with Duphaston in threatened and habitual abortion have shown promising results. In one study, Duphaston was given in increasing doses from 2.5 to 20mg/day, depending on the clinical condition and the hormonal levels that were routinely determined in the second or third month of pregnancy. In a large number of patients, Duphaston was combined with synthetic oestrogens. Treatment was started early in pregnancy, and the duration varied from a few weeks to several months. The study showed highly favourable results with Duphaston. Out of 111 evaluable cases, there were 102 deliveries.87

In a randomised, placebo- and reference-controlled study by El-Zibdeh, a total of 114 patients with habitual abortion received either Duphaston (10mg twice daily, n=48), hCG (5000 IU intramuscularly every 4 days, n=36) or no treatment at all (n=30). Treatment was started as soon as possible after pregnancy was confirmed, and continued until the 12th gestational week. Duphaston showed a 27% relative reduction in the abortion rate compared to the control group (p<0.05).87

Freedman and Berry studied 31 women with a history of habitual abortion, or other fertility problems, who were all progesterone-deficient as demonstrated by vaginal cytology. Eighteen patients were treated with Duphaston, whilst 13 controls received no treatment. 67% of the Duphaston patients (n=12) had successful deliveries, compared to 8% (n=1) in the control group.88

The overall success rate of Duphaston in several smaller, older studies was 81%. In 8% of all cases, there were other confirmed, or suspected underlying causes that led to abortion.

Threatened abortion

A second randomised placebo-controlled study by El-Zibdeh, looked at the benefits of Duphaston in threatened abortion. A total of 146 patients received either Duphaston (10mg twice daily, n=86), or no treatment at all (n=60). Duphaston reduced the abortion rate by 30% in comparison to the control group (p<0.05).88-90

Compared with other hormonal therapies, Duphaston® is especially recommended in threatened and habitual abortion because it is non-virilising and has no adverse effects on the foetus.91

Duphaston®, well-absorbed and with stable bio-availability, is also devoid of the hepatic side-effects that are seen with oral progesterone.92,93

A recent risk/benefit assessment of the exposure of the foetus to dydrogesterone (Duphaston) showed that there is no major concern regarding the risk profile of dydrogesterone when administered to pregnant women.
Duphaston® in Endometriosis

Endometriosis is characterised by the presence of endometrial glands and cytogenic stroma in extra-uterine locations. It is a chronic benign disease with a high risk of recurrence, despite treatment. The aetiology of the disease, however, is poorly understood. Endometriosis affects approximately 10% of premenopausal women, and can cause severe, progressive, and at times, incapacitating dysmenorrhoea, as well as pelvic pain, dyspareunia and infertility. Patients are usually diagnosed between 20 and 40 years of age, but about 10% of cases occur under the age of 20. Endometriosis may persist during the entire reproductive life of a woman.95

Many investigators have attempted to explain the pathophysiology of endometriosis-associated pain. Although the number and severity of the lesions are not thought to correlate with the severity of the symptoms, the total number of ectopic endometrial implants does appear to be related to the intensity of pain.96-98

Currently danazol or GnRH analogues are believed to be the most effective treatment of endometriosis besides surgery. However, in many cases, symptomatic treatment with low doses of progestogens may be sufficient, especially since they have the added benefit of fewer side-effects. Although scientific data concerning their mechanism are not fully understood, their use has proved effective for several decades. One possible mechanism is thought to occur via initial decidualisation of endometrial tissue and eventual atrophy.99

As pain may be caused by the secretion of prostaglandins, even by very small lesions, progestogens may also be effective in bringing pain relief by reducing the synthesis of prostaglandins. Reducing the number and size of the lesions is not crucial for this relief to take effect.100

The efficacy of synthetic progestogens in the treatment of endometriosis was first described in 1958.101 These earlier treatment regimens were aimed at inducing ‘pseudopregnancy’ and were associated with a high incidence of side-effects and consequently low compliance. Since then, a number of trials have been conducted to investigate the efficacy of lower doses of better tolerated progestogens.

In a recent, randomised, double-blind, placebo-controlled study in 62 women, Duphaston was shown to be effective in the treatment of mild endometriosis. Duphaston significantly improved pain scores.102 Similarly, the data from four baseline controlled studies showed that the majority of patients became symptom-free or experienced a significant reduction in the occurrence and severity of symptoms.103-106 Regression of lesions was also reported, although the extent to which these disappeared differed across studies.

Several recent critical appraisals of the treatment of endometriosis valued the use of progestogens for temporary relief of endometriosis-associated pelvic pain107 and their effect was comparable with other drugs such as GnRH agonists and danazol. However, the latter cause more side-effects and are more expensive.

The efficacy of medical treatment (including progestogens) on the disappearance or regression of lesions and pregnancy rates in infertile women is less clear. Recurrence rates of up to 55% at 6 months have been reported after discontinuation of treatment. Since it is a chronic disease, treatment needs to be repeated and long-term, and a such, it should also be well-tolerated. This is not the case, however, with danazol (due to its androgenic side-effects), nor with GnRH-analogs (as they induce ‘artificial menopause’, thereby producing vasomotor symptoms and bone loss).95,96,99,108-111

In contrast, Duphaston® has few and usually mild side-effects in endometriosis, and is therefore particularly recommended.112
Duphaston® in Premenstrual Syndrome

Premenstrual syndrome (PMS) is a disorder characterised by a range of mood swings and physical symptoms. Most women experience some premenstrual changes. Between 20-40% report some degree of physical or psychological symptoms. The cause of these symptoms is unclear and may be multi-factorial. What is certain however, is that PMS is partly related to the ovarian hormonal fluctuations of the menstrual cycle.

Typical somatic symptoms of PMS include breast discomfort, weight gain, abdominal distension and headache. Depression, tension, anxiety and inability to concentrate are frequently reported psychological symptoms. These usually begin after ovulation in the second half of the cycle, and are most apparent during the luteal phase. Symptoms are completely relieved at the time of menstruation with relief lasting a minimum of 1 week.

To date, no ideal method has been designed for diagnostic assessment of the various aspects of the syndrome. Neither has any single treatment emerged that is effective against all symptoms. The multi-factorial nature of PMS, the absence of a clear definition of what constitutes a therapeutic effect, as well as the usually observed high placebo response (as much as 30 to 50%), render the evaluation of therapeutic efficacy extremely difficult. In randomised double-blind clinical trials, only a few treatments have been shown to be superior to placebo.

Progestrone was first advocated for use in PMS in 1938 by Israel. His recommendation was based on a theory of progesterone deficiency and imbalance of ovarian hormones. The efficacy of Duphaston in PMS has been documented by, amongst others, Haspels who reported the results of 150 patients who took part in a double-blind, placebo-controlled, multi-national study. The patients were observed during four consecutive menstrual cycles. The first cycle was a baseline cycle, and in the three subsequent cycles, patients were given either 10mg Duphaston twice daily, or placebo from day 12 until the first day of the next menstruation. Based on evaluable results from 123 patients (70 on Duphaston, 53 on placebo), the author concluded that Duphaston was more effective than placebo against psychological symptoms, and clinically better against somatic symptoms. Duphaston was also more effective in moderate and severe cases. These beneficial effects of Duphaston have been confirmed by many others.

When PMS is associated with hypermenorrhoea and dysmenorrhoea, Duphaston® is a treatment of choice.
**Duphaston® in HRT**

**Menopause and Postmenopause**

Though varying widely by region and country, the average life expectancy of women has greatly increased over the last century. Because of this, a woman’s postmenopausal period also lasts longer. Indeed, in developed countries, it may span about a third of a woman’s life. The loss of circulating oestrogens during the menopause has a variety of adverse consequences, ranging from the inconvenient (flushes and night sweats) to the potentially life-threatening (cardiovascular disease and osteoporosis).

The most likely reason for initial consultation is the frequent occurrence of vasomotor symptoms and mood changes (climacteric syndrome). This syndrome is characterised by hot flushes, night sweats, fatigue, palpitations, headaches, as well as anxiety, irritability and forgetfulness, difficulty in concentrating and a general lack of confidence. It is estimated that as many as 85% of women suffer from some of these symptoms at the time of menopause, and that 30% are severely affected by them. For the majority, the duration of these complaints lasts between 2 and 8 years.

Other symptoms may arise after prolonged oestrogen deficiency, such as tissue changes in the genital tract and bladder, with alterations in sexual function and urinary symptoms. Indeed, 15 to 50% of postmenopausal women suffer from some form of urogenital symptoms. Certainly, oestrogens have a major impact on bone tissue, contributing to a balanced bone mass, strength and elasticity. Oestrogen depletion at menopause leads to bone resorption and eventually to the loss of trabecular plates (postmenopausal osteoporosis). The annual rate of bone loss in the first 5 years after menopause is estimated to be between 3 and 5%. This loss can lead to an increase in hip, spinal, wrist and other bone fractures later in life. These osteoporosis-related fractures have a considerable impact not only on quality of life, but also on health expenditure. Prevention of osteoporosis is therefore essential since, although bone mass can be regained in part, loss of connectivity cannot be restored once it has been destroyed.

There is also considerable evidence of a link between loss of ovarian function and increased risk of cardiovascular disease. Before middle-age, death due to cardiovascular disease is infrequent in women, but not in men (ratio 1:5, women:men). From the age of 55 onwards, however, mortality figures rise more rapidly in women, and by the age of 85, the gender ratio is actually inverted (ratio 2.5:1, women:men). It would appear, therefore, that oestrogen is an important protective factor against cardiovascular disease in women. Whilst its underlying mechanisms are not fully understood, it seems that oestrogen depletion may be related to adverse metabolic changes causing atherosclerosis.
HRT

The aim of oestrogen replacement therapy is to increase the circulating levels of oestrogens to control hot flushes and to prevent the long-term effects of the menopause.188,196 For the majority of menopausal women, HRT offers an opportunity to significantly improve quality of life.

A recent pharmacoeconomic evaluation found that HRT is a highly cost-effective treatment for the symptoms of the climacteric syndrome.186

Morbidity, mortality and cost factors have been frequently quoted as justification for the preventive treatment of postmenopausal osteoporosis.146,158,159 Oestrogen replacement therapy has been shown unequivocally to reduce the incidence of osteoporotic fractures.146,158-159 Epidemiological surveys have shown that HRT reduces the incidence of fractures by 20 to 45%.180,183,196 The results from a large retrospective, multi-centre, population-based study in 2,086 women with hip fractures and 3,532 age-matched controls showed that HRT was superior in preventing hip fractures compared to other regimens e.g. calcium preparations, anabolic steroids, calcitonins or vitamin D compounds.159 Recently, the reduction of fracture risk by HRT was proven by a large prospective study.160 Because bone loss recurs when oestrogens are withdrawn, the prevention of osteoporosis may need to be continued until age 70, and occasionally beyond.184,185

Oestrogens stimulate the growth of endometrial cells. Therefore, oestrogen monotherapy in postmenopausal women results in endometrial proliferation without the physiological secretory transformation induced by progesterone. This process is associated with an increased incidence of endometrial hyperplasia and carcinoma.170,171

Additional treatment with progestogens is therefore mandatory in women with an intact uterus who receive oestrogen replacement therapy.172-174,176 All currently available progestogens, provided they are used at an adequate dose and for an adequate duration, are effective in protecting the endometrium from the proliferative effects of oestrogen monotherapy. The use of Duphaston and other progestogens in HRT is therefore only indirectly associated with HRT indications.

Any progestogen used in HRT should have a well-documented safety profile to avoid undermining the beneficial effects of oestrogen replacement therapy.

**Duphaston**, unlike some of the more androgenic progestogens, has no detrimental effect on favourable oestrogen-induced changes in lipid profile or on carbohydrate metabolism. Nor does Duphaston adversely affect oestrogen-induced prevention of bone loss.

The addition of Duphaston to oestrogen replacement therapy does not antagonise the beneficial effects of oestrogens on acute climacteric symptoms.

Osteoporosis

The effects of oestrogen supplementation on bone are well documented, and seem to be linked to dosage.188,196,198-200 Bone reduction generally occurred with placebo or no treatment. Reduction of bone turnover is the primary mechanism of action of oestrogen in preventing postmenopausal bone loss, though other mechanisms may also be involved.202 Studies of serum oestradiol levels have shown a significant reduction in bone resorption (measured by urinary calcium:creatinine and hydroxyproline:creatinine ratios) is achieved when circulating levels of oestrogens are similar to those seen in premenopausal women during the follicular phase.227

Oestrogen replacement therapy has been shown to reduce both vasomotor and psychological symptoms, and to generally improve quality of life.177,194 The addition of Duphaston does not antagonise the beneficial effects of oestrogens on acute climacteric symptoms.191-198

**Figure 14**

Clear and persistent reduction of menopausal symptoms194 (Femoston® contains 17ß-oestradiol and dydrogesterone, in a sequential regimen)

- Baseline
- 6 weeks Femoston®
- 12 weeks Femoston®
- 52 weeks Femoston®

Combined HRT also improves vaginal symptoms;196,197 which may lead to enhanced coital satisfaction and sexual desire.201,202
The effects of Duphaston on the incidence of fractures has not been assessed. However, clinical studies measuring bone mineral density (BMD), which is considered to be the most accurate predictor of fracture risk in postmenopausal women, indicate that Duphaston does not affect the protective properties of oestrogens on bone.233,236-238

Starting HRT during, or shortly after the menopause is more effective in preventing bone loss and fractures, than starting it later in life. This is because bone trabeculae which have already been destroyed cannot be regrown. However, the benefits of HRT on bone are not diminished in older women.186,195,206,208,209 Increases in BMD and reductions in fracture risk can also be obtained in those who start HRT many years after the menopause.235

**Cardiovascular Risk Factors**

**Plasma lipid and lipoprotein profile**

Oral oestrogens increase high-density lipoprotein (HDL) cholesterol serum levels and decrease low-density lipoprotein (LDL) cholesterol. They also decrease lipoprotein(a) (Lp(a)) - a highly atherogenic lipoprotein that structurally resembles LDL. Serum HDL cholesterol is inversely related to cardiovascular risk.

A recent review of 248 prospective studies published between 1974 and 2000 shows that some progestogens partly reverse the beneficial effects of oral oestrogen replacement on lipids. They do this by reducing HDL cholesterol, thereby reducing the cardiovascular benefits obtained with oestrogen alone.234,191,193,196,224,234-245

Duphaston has no adverse effect on lipid profiles. Hence it does not diminish the cardiovascular benefits obtained with oral oestrogen therapy.23,196,224,236,246-251

Indeed, clinical studies prove that lipid profiles obtained with combined oestradiol/Duphaston HRT are good, and that the magnitude of the effect matches that of unopposed oral 17ß-oestradiol.196,224,236,246-251

The beneficial effects of HRT for primary prevention of cardiovascular disease have been challenged recently. In a double-blind, placebo-controlled prospective trial in over 16,500 postmenopausal women who were followed for more than five years, those on HRT had a slightly higher incidence of heart attack and stroke than controls.160 This difference was however restricted to the combination of oestrogen with medroxyprogesterone acetate, the progestogen used in the study. Duphaston has a better cardiovascular safety profile than medroxyprogesterone acetate.244

The efficacy of HRT in secondary prevention has been challenged by the HERS-study, and more recently by its long term follow-up (HERS II).252,253 These studies showed that HRT did not reduce the risk of cardiovascular events in postmenopausal women who already had cardiovascular disease.
Body weight
Excess weight and obesity are linked to increased morbidity and mortality. In particular, the central distribution of fat is considered as an independent predictor of cardiovascular disease in women. Evidence suggests that throughout the climacteric period increased body weight and a shift towards a more central, android fat distribution occurs in women of normal weight. By contrast, Duphaston has no impact on carbohydrate metabolism, and preserves the positive effects of oestrogens.

Carbohydrate metabolism
Insulin resistance, impaired glucose tolerance and hyperinsulinaemia may result from postmenopausal oestrogen deficiency, and increase the risk of cardiovascular disease. Oestrogen replacement therapy can maintain all these parameters at premenopausal levels, but the effect of some progestogens used in combined HRT may reduce the overall benefits. Androgenic progestogens, in particular, have a negative effect on glucose tolerance and raise plasma insulin levels. By contrast, Duphaston has no impact on carbohydrate metabolism, and preserves the positive effects of oestrogens.

Homocysteine concentration
Elevated plasma levels of homocysteine, as observed in postmenopausal women, is an independent risk factor for cardiovascular disease and thrombosis. Homocysteine damages the vascular endothelial cells, thus contributing to a higher risk of atherothrombosis. Plasma homocysteine levels are low in premenopausal women, but increase after menopause, suggesting a close connection between homocysteine metabolism and oestrogen status. This is probably one of the mechanisms through which menopause unfavourably affects cardiovascular disease in postmenopausal women.

Oestrogen replacement therapy significantly lowers plasma homocysteine, an independent cardiovascular risk factor. This favourable effect is not reduced with combined 17β-oestradiol/dydrogesterone (Duphaston).

Coagulation and fibrinolysis
Whether progestogens affect coagulation parameters depends on the type of progestogen, the dosage and the route of administration. Clotting factors, including platelet adhesiveness, are not affected by Duphaston.

Blood pressure
The effects of Duphaston on blood pressure have hardly been investigated. Studies on HRT have either reported no change, or just a small decrease in normotensive women. On the other hand, a decrease (as much as 11mmHg and 9mmHg in diastolic and systolic blood pressure, respectively) was reported in normotensive women who were given combined oestrogen/Duphaston HRT.

Duphaston preserves the positive effects of oestrogens

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Duphaston combined with oral oestradiol
- Diminishes the accumulation of central body fat
- Decreases total lean body mass compared with controls

Figure 16 Impact of various HRT regimens on fat distribution

Body weight
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Duphaston®: Safety and Tolerability

Duphaston was first introduced to the market in 1961, and is currently approved in over 100 countries world-wide. It has an estimated cumulative exposure of more than 28 million patients. Duphaston is safe and well-tolerated. Occasionally breakthrough bleeding may occur, but the incidence of other side-effects is remarkably low.

Duphaston is not chemically related to testosterone and has a low affinity for the androgen receptor. Even at high doses and after prolonged treatment, therefore, it does not cause unwanted androgenic side-effects such as voice changes, hirsutism and acne in the adult female, nor masculinisation of the female foetus.5,14

Duphaston has a well-documented anti-oestrogenic activity on the endometrium, but has no intrinsic oestrogenic effects. No oestrogenic priming has been observed in clinical practice. Also, if given early in life, Duphaston has no adverse effects on fertility or sexual development.14,16

Duphaston does not interfere with normal ovulation as demonstrated by:11,12,19-21
• normal rises in oestrogen and pregnanediol
• cytological evidence of ovulation
• normal premenstrual biopsy
• no modification of vaginal cytology
• formation of the corpus luteum (confirmed at laparotomy).

Duphaston does not change the basal temperature, and as such ovulation can still be detected. Therapeutically effective doses of Duphaston can be used in women who wish to become pregnant. There is no major concern regarding the risk of dydrogesterone (Duphaston) when administered to pregnant women. Duphaston has no adverse effects on glucose tolerance or blood lipids, no significant effects on blood coagulation or liver function, and none on body weight or blood pressure.22-24,191,193,196,224,235-245,247,248,261-266,274,280-283

The strength of HRT is determined not only by its relief of climacteric symptoms, but also by its ability to prevent the long-term sequelae of oestrogen deficiency. As such, the safety and tolerability of HRT are essential factors that allow successful prevention of disease. Safety (i.e., endometrial safety) and tolerability (i.e., bleeding pattern) of HRT are determined primarily by the progestogen used.

Bleeding Patterns

The type and severity of bleeding pattern (i.e., in terms of the number and regularity of bleeding episodes) are important factors affecting compliance, as the re-establishment of premenopausal bleeding patterns, or the occurrence of irregular bleeding are the main reasons given for either not starting, or discontinuing HRT.284-290

In perimenopausal patients, the addition of a sequential progestogen in HRT aims at the recurrence of regular vaginal bleeding. Duphaston is associated with light, regular and highly predictable bleeds. A combined oestradiol/Duphaston regimen gives favourable bleeding patterns in menopausal and perimenopausal patients.10,191,291-296 Results for Duphaston are favourable in comparison with other progestogens, such as medroxyprogesterone acetate.214

HRT regimens with continuous administration of oestrogens and progestogens are expected to induce amenorrhoea in postmenopausal patients, but can be associated with breakthrough bleedings.297 It seems that oestrogen is the determining factor in the incidence of bleeding during postmenopausal HRT.
Endometrial Safety

The expected incidence of hyperplasia in untreated women is 1 to 2% per year.300,301,302

A recent case-control study in 709 postmenopausal patients with endometrial carcinoma and 3,368 control subjects, showed that additional progestogen clearly lowers the risk of carcinoma, compared with unopposed oestrogen replacement.303 The odds ratio for risk of endometrial carcinoma after 5 or more years of treatment was 6.2 with unopposed oestradiol treatment, but only 0.2 with continuously combined oestrogen/progestogen treatment.

The combined incidence of hyperplasia and carcinoma is clearly lower in studies where Duphaston is sequentially combined with 17ß-oestradiol. The endometrial safety of Duphaston in this combination has recently been assessed in a meta-analysis of four studies.304 Safety was assessed by endometrial biopsy in 369 women, of whom 256 were treated for at least 12 months. With the Duphaston/17ß-oestradiol combination, there were no cases of endometrial cancer, and only one case of simple hyperplasia without atypical cytological changes. This corresponds with a success rate of 99.7%, within the criteria established by the CPMP.305

High success rates were also reported when Duphaston (2.5-20mg/day) was continuously combined with 17ß-oestradiol 1mg (n=718) or 2mg (n=368).306 No cases of endometrial hyperplasia were reported.

**Duphaston© effectively protects the endometrium against the development of hyperplasia.**305,306

Risk of Breast Cancer with HRT

Along with lung cancer, breast cancer is the commonest form of malignancy in women. There is a progressive risk increase with age, and the cumulative lifetime risk of breast cancer for a woman who lives past 85 is roughly 10%.155

Besides genetic factors, early menarche and late menopause increase the risk of breast cancer.

Breast cancers in current or recent users of HRT are less likely to spread outside the breast compared to those found in non-users. Women who develop breast cancer after HRT tend to have less aggressive tumours and possibly better survival chances compared to those who do not receive HRT.307-312

The associations between long-term HRT exposure and increased risk of breast cancer may be due to earlier diagnosis, to an actual effect of HRT, or to a combination of both.

Progesterone derivatives like Duphaston can inhibit the enzymes that convert oestrone sulphate to oestradiol in breast tissue, and may therefore help reduce the risk of breast cancer.313-315
Duphaston (dydrogesterone) is a potent, orally active progestogen which is used to great effect in a wide variety of gynaecological conditions. These include: menstrual disorders, infertility, threatened and habitual abortion, endometriosis, premenstrual syndrome and HRT.

The use of Duphaston is closely related to its physiological action on both the neuroendocrine control of ovarian function and the endometrium, and as such Duphaston is indicated in all cases where there is relative or absolute endogenous progesterone deficiency.

Although similar in molecular structure and pharmacological effects to endogenous progesterone, Duphaston has the advantage of being orally active at far lower dosages. In addition, because of its selectivity for the progesterone receptor, no undesirable hormonal effects are expected. Its freedom from oestrogenic, androgenic, anabolic, corticoid and other undesirable hormonal effects gives it substantial benefits over other synthetic progestogens. There is no major concern regarding the risk profile of Duphaston when administered to pregnant women.

No serious or unexpected toxicity has been observed with Duphaston, nor has it shown any mutagenic potential. Duphaston also has no adverse effects on glucose tolerance or blood lipids, no significant effects on blood coagulation or liver function, and none on body weight or blood pressure. Favourable results that are highly significant, particularly in the context of long-term therapy.

As well as its broad applicability and efficacy, Duphaston is a treatment that has earned widespread trust. Currently approved in over 100 countries worldwide, experience in 28 million patients has confirmed the safety and tolerability of Duphaston.

Conclusion

Duphaston®

- Designed to be Orally Active
  - Fast and well-absorbed
  - Predictable bio-availability
  - Orally active at low dosages

- Designed to be Well-tolerated
  - Easy absorption and stable bio-availability means better tolerability
  - Does not induce drowsiness
  - Places no extra burden on the liver
  - Does not cause acne, seborrhoea, alopecia or hirsutism

- Designed to be Safe
  - Highly specific, without unwanted androgenic or anti-androgenic effects, even at high doses and after prolonged treatment
  - No effect on ovulation at recommended doses, nor on the fertility of the offspring
  - No major concern regarding the risk profile of dydrogesterone when administered to pregnant women
  - Free from adverse effects on carbohydrate metabolism
  - No changes in body weight, blood pressure, glucose tolerance or blood lipid ratios
  - Does not increase thrombotic risk

- Designed to be Convenient
  - Oral progesterone is more effective and more convenient than vaginal products

- Designed to be Effective
  - Relieves symptoms of dysmenorrhoea
  - Induces withdrawal bleedings in secondary amenorrhoea
  - Arrests heavy menstrual bleeding and regulates the menstrual cycle in patients with DUB
  - High success rates in infertility due to luteal deficiency, in threatened and habitual abortion
  - Significantly reduces occurrence and severity of symptoms in endometriosis
  - Treatment of choice when PMS is associated with hypermenorrhoea and dysmenorrhoea
  - In HRT
    - Associated with light, regular, highly predictable bleeds in sequential regimens
    - Induces amenorrhoea in continuously combined regimens
    - Does not antagonise the beneficial effects of oestrogens on climacteric symptoms
    - Does not diminish the protective effects of oestrogens on bone
    - Protects the endometrium against hyperplasia
Duphaston® Posology

6
**Duphaston® Posology**

**Dysmenorrhoea**
Duphaston
10mg twice daily

**Secondary amenorrhoea**
Duphaston
10mg twice daily

**Dysfunctional uterine bleeding**
Duphaston
10mg twice daily for 5 to 7 days

**Irregular cycles**
Duphaston
10mg twice daily

**Infertility**
(due to luteal insufficiency)
Duphaston
10mg once daily, for at least 6 consecutive cycles

**Habitual abortion**
Duphaston
10mg twice daily until the 20th week of pregnancy

**Threatened abortion**
Duphaston
40mg immediately, then 10mg every 8 hours until symptoms remit

**Endometriosis**
Duphaston 10mg, twice or thrice daily from day 5 to 25 or continuously

**Premenstrual syndrome**
Duphaston
10mg twice daily

**Hormone replacement therapy**

- **Perimenopause**
oestrogen, continuously
  - Duphaston
  10mg once daily

- **Postmenopause**
oestrogen, continuously
  - Duphaston
  5mg once daily, continuously

*These treatment schedules are available in fixed combination as Femoston® and Femoston® conti: Femoston®: 1 or 2mg 17β-oestradiol + 10mg dydrogesterone, in a sequential regimen Femoston® conti: 1mg 17β-oestradiol + 5mg dydrogesterone, continuously*
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Pharmacological Properties:

Dydrogesterone is an orally-active progestogen which is indicated in all cases of endogenous progesterone deficiency. Dydrogesterone has no anabolic or corticoid activity.

Preclinical safety data: Dydrogesterone has been used in several animal models and has been proven to be an entity with low toxicity, not having mutagenic or carcinogenic properties. No effects were seen in reproduction experiments. Shelf life: 5 years.

Special precautions for storage: Store in a dry place, not below 0°C or above 30°C, in the original package. Keep out of the reach of children.

Date of approval/revision of this SMPC text: April 16, 2002

For more details on Femoston® and Femoston® conti, see their prescribing information. Further information is available on request from Solvay Pharmaceuticals.

Designed and typeset by FCB GLOBAL HEALTHCARE, 1030 Brussels, Belgium.