SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Norgeston*

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

35 hormone-containing white tablets

Each tablet contains:

Actives:Levonorgestrel 30 micrograms

Excipients with known effect:
Lactose 33.12mg
Sucrose 19.66mg

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated tablet

White, round, biconvex coated tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral contraception

4.2 Posology and method of administration

First treatment cycle: One tablet daily, starting on the first day of the menstrual cycle, at a time of day chosen by the patient. All subsequent tablets must then be taken at this time. The contraceptive effect is likely to be reduced if a tablet is delayed by more than three hours. Additional contraceptive precautions are not necessary when initiating treatment.

Subsequent cycles: The tablets are taken daily and pack follows pack without interruption, and without regard to bleeding.

Changing from a combined oral contraceptive (COC), vaginal ring, or transdermal patch: If the woman has correctly and consistently used the previous COC, the first tablet of Norgeston should be taken on the first day after the last active tablet of the COC pack (In the case of every day (ED) tablet use, the inactive ones should be omitted). If a vaginal ring or transdermal patch has been used correctly and consistently before the switch, the woman should start using Norgeston on the day of removal of the last vaginal ring or transdermal patch of a cycle pack and thereby omit the hormone-free interval of this product. Additional contraceptive precautions are not required.

Changing from another POP: The switch can be made at any time without interruption of contraceptive protection.

Changing from a progestogen-only parenteral method (implant, injection): The switch should be made before or when the next injection or implant is due.

Post-partum use: Norgeston can be initiated up to 21 days post-partum (no additional contraceptive is required). If started after 21 days additional barrier contraceptive methods should be used for 7 days. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of Norgeston use or the woman has to wait for her first menstrual period. For additional information on breast feeding women see section 4.6

Post-abortion or miscarriage use After a first trimester abortion, Norgeston may be started at the time of the abortion or miscarriage. Additional contraceptive precautions will not then be required. If started after this time barrier contraceptive methods should be used for 7 days.

Special circumstances requiring additional contraception:

Management of missed pills: If the user forgets a pill she should take it as soon as she remembers and carry on with the next pill at the same time. If the pill was more than 3 hours overdue (> 27 hours since the last pill was taken) she will not be protected from pregnancy. She should continue normal pill taking but must also use barrier contraceptive methods for the next 7 days. If intercourse took place in the preceding 7 days, the possibility of a pregnancy should be considered. The more tablets are missed, the higher the risk of a pregnancy.

Gastro-intestinal upsets: If vomiting occurs within 2 hours of taking a tablet, another pill should be taken as soon as possible. If a replacement pill is not taken within 3 hours of the scheduled time, additional, barrier contraceptive methods should be used for 7 days.

In cases of persistent vomiting and/or very severe diarrhoea, additional barrier contraceptive methods should be used during the illness and for 7 days after recovery.

Paediatric population
There is no relevant indication for the use of Norgeston before menarche

Geriatric patients
Not applicable. Norgeston is not indicated after menopause.

Patients with hepatic impairment
Norgeston is contraindicated in women with severe hepatic diseases. See also section 4.3.

Patients with renal impairment

Norgeston has not been specifically studied in renally impaired patients.

4.3 Contraindications

Norgeston should not be used in the presence of any of the conditions listed below. Should any of the conditions appear during the use of Norgeston, the use of the preparation must be discontinued immediately.

- Known or suspected pregnancy.
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
- History of or existing thromboembolic processes (e.g. stroke, myocardial infarction).
- Presence or history of liver tumours (benign or malignant).
- Known or suspected sex- steroid influenced malignancies (e.g. current or history of breast cancer).
- Undiagnosed abnormal vaginal bleeding.
- Severe diabetes with vascular changes.
- Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Medical Examination

Assessment of women prior to starting oral contraceptives (and at regular intervals thereafter) should include a personal and family medical history of each woman. Physical examination should be guided by this and by the contraindications (section 4.3) and warnings (section 4.4) for this product. The frequency and nature of these assessments should be based upon relevant guidelines and should be adapted to the individual woman, but should include measurement of blood pressure.

Exclude the likelihood of pregnancy before starting treatment.

Warnings

The benefits of using Norgeston should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start using it. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her physician. The physician should then decide on whether Norgeston should be discontinued.

Women should be advised that oral contraceptives do not protect against HIV infections (AIDS) and other sexually transmitted diseases.

Reasons for stopping Norgeston immediately.

When stopping oral contraception non-hormonal contraception should be used to ensure contraceptive protection is maintained.

1. Occurrence for the first time, or exacerbation, of migrainous headaches or unusually frequent or unusually severe headaches.
2. Sudden disturbances of vision or hearing or other perceptual disorders.
3. First signs of thrombophlebitis or thromboembolic symptoms (for example, unusual pains in or swelling of the legs, stabbing pains on breathing or coughing for no apparent reason), feeling of pain and tightness in the chest.
4. Six weeks before an elective major operation (e.g. abdominal, orthopaedic) any surgery to the legs, medical treatment for varicose veins or prolonged immobilisation e.g. after accidents or surgery. Do not restart until 2 weeks after full ambulation. In case of emergency surgery, thrombotic prophylaxis is usually indicated e.g. subcutaneous heparin.
5. Onset of jaundice, hepatitis, itching of the whole body.
6. Clear exacerbation of conditions known to be capable of deteriorating during oral contraception or pregnancy (e.g. recurrence of cholestatic jaundice and/or pruritus which occurred first during pregnancy or previous use of sex steroids).
7. Pregnancy is a reason for stopping immediately because it has been suggested by some investigations that oral contraceptives taken in early pregnancy may slightly increase the risk of foetal malformations. Other investigations have failed to support these findings. The possibility therefore cannot be excluded, but it is certain that if a risk exists at all it is very small.

Circulatory Disorders

In the few epidemiological studies conducted, which are limited in the number of subjects, there is little evidence for an association between progestogen only pills and an increased risk of myocardial infarction and cerebral thromboembolism. The risk of cardiovascular and cerebral events is rather related to increasing age, hypertension, and smoking. In women with hypertension the risk of stroke may be slightly enhanced by progestogen-only pills.

There may be a slightly, but not statistically significant increased risk of venous thromboembolism (deep venous thrombosis, pulmonary embolism) associated with the use of progestogen-only pills. Generally recognized risk factors for venous thromboembolism (VTE) include a positive personal or family history (VTE in a sibling or a parent at a relatively early age), age, obesity and prolonged immobilization, major surgery or major trauma.

Tumours

- *Breast Cancer*

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk of having breast cancer diagnosed in women who are currently using oral contraceptives (OC). The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in OC users, the biological effects of OCs or a combination of both. The additional breast cancers diagnosed in current users of OCs

or in women who have used OCs in the last 10 years are more likely to be localised to the breast than those in women who never used OCs.

Breast cancer is rare among women under 40 years of age whether or not they take OCs. Whilst the background risk increases with age, the excess number of breast cancer diagnoses in current and recent progestogen-only pill (POP) users is small in relation to the overall risk of breast cancer, possibly of similar magnitude to that associated with combined OCs. However, for POPs, the evidence is based on much smaller populations of users and so is less conclusive than that for combined OCs. Available studies do not provide evidence for causation.

The most important risk factor for breast cancer in POP users is the age women discontinue the POP; the older the age at stopping, the more breast cancers are diagnosed. Duration of use is less important and the excess risk gradually disappears during the course of the 10 years after stopping POP use, such that by 10 years there appears to be no excess.

The evidence suggests that compared with never-users, among 10,000 women who use POPs for up to 5 years but stop by age 20, there would be much less than 1 extra case of breast cancer diagnosed up to 10 years afterwards. For those stopping by age 30 after 5 years use of the POP, there would be an estimated 2-3 extra cases (additional to the 44 cases of breast cancer per 10,000 women in this age group never exposed to oral contraceptives). For those stopping by age 40 after 5 years use, there would be an estimated 10 extra cases diagnosed up to 10 years afterwards (additional to the 160 cases of breast cancer per 10,000 never-exposed women in this age group).

It is important to inform patients that users of all contraceptive pills appear to have a small increase in the risk of being diagnosed with breast cancer, compared with non-users of oral contraceptives, but that this has to be weighed against the known benefits.

- *Liver Cancer*

In rare cases benign, and in even rarer cases, malignant liver tumours leading in isolated cases to life-threatening intra-abdominal haemorrhage have been observed after the use of hormonal substances such as the one contained in Norgeston. If severe upper abdominal complaints, liver enlargement or signs of intra-abdominal haemorrhage occur, a liver tumour should be included in the differential diagnostic considerations.

Other conditions

- *Diabetes*

Diabetes mellitus or tendency towards diabetes mellitus requires careful medical supervision.

- *Ectopic Pregnancy*

If there is a history of ectopic pregnancy or one Fallopian tube is missing, the use of Norgeston should be decided on only after carefully weighing the benefits against the risks.

If obscure lower abdominal complaints occur together with an irregular cycle pattern (above all amenorrhoea followed by persistent irregular bleeding), an extrauterine pregnancy must be considered.

- *Persistent ovarian follicles*

Persistent ovarian follicles (often referred to as functional ovarian cysts) may occur during the use of Norgeston. Most of these follicles are asymptomatic, although some may be accompanied by pelvic pain or dyspareunia. In most cases, the enlarged follicles disappear spontaneously during two to three months of observation.

- *Psychiatric disorders*

Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use (see section 4.8). Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

- *Chloasma*

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking Norgeston.

- *Lactose and Sucrose intolerance*

Each tablet of this medicinal product contains 33.12 mg lactose and 19.66 mg sucrose per tablet. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, fructose intolerance or glucose-galactose malabsorption or sucrase-isomaltase should not take this medicine.

- *Bleeding patterns*

Menstrual changes: A usual feature of all progestogen-only oral contraceptives is that they can produce an initial irregularity of the bleeding pattern, but such irregularity tends to decrease with time. Some women may experience amenorrhoea.

For these reasons the possibility of such changes in menstrual rhythm should, as a precaution, be pointed out to the patient before the start of tablet-taking.

Amenorrhoea / Missed menstruation: If no menstrual bleeding has occurred within 6 weeks after the last menstrual bleeding, pregnancy must be excluded before tablet-taking is continued. If pregnancy has been excluded and the amenorrhoea lasts longer than 3 months or recurs repeatedly, Norgeston should be withheld until normal menstrual bleeding has been restored.

Procedure in the event of irregular bleeding: Irregular bleeding is not a medical reason for stopping tablet-taking, as long as organic causes for such bleeding and pregnancy can be ruled out provided it is ensured that the patient is fully compliant.

It is extremely inadvisable to attempt to influence cycle disturbances by the additional administration of an oestrogen. This would only serve to reverse the changes brought about by Norgeston in the cervical mucus, thereby seriously reducing the contraceptive effect.

4.5 Interaction with other medicinal products and other forms of interaction

Note: The prescribing information of concomitant medications should be consulted to identify potential interactions.

Effects of other medicinal products on Norgeston

Interactions can occur with drugs that induce microsomal enzymes, which can result in an increased clearance of sex hormones and which may lead to breakthrough bleeding and oral contraceptive failure. This has been established with many hepatic enzyme-inducing drugs.

Enzyme induction can be observed after a few days of treatment. Maximal enzyme induction is generally seen within a few weeks. After the cessation of drug therapy enzyme induction may be sustained for about 4 weeks.

Short-term treatment
Women on treatment with enzyme-inducing drugs should temporarily use a barrier method or another method of contraception in addition to Norgeston. The barrier method must be used during the whole time of the concomitant drug therapy and for 28 days after its discontinuation. If the drug therapy runs beyond the end of the tablets in the Norgeston pack, the next Norgeston pack should be started right after the previous one.

Long-term treatment
In women on long-term treatment with hepatic enzyme-inducing active substances, another reliable, non-hormonal, method of contraception is recommended.

Substances increasing the clearance of levonorgestrel (diminished efficacy of Norgeston by enzyme-induction), e.g.:

Phenytoin, barbiturates, primidone, carbamazepine, rifampicin and possibly also oxcarbazepine, topiramate, felbamate, griseofluvin and products containing St. John's wort (*Hypericum perforarum*).

Substances with variable effects on the clearance of levonorgestrel

When co-administered with sex hormones, many HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of the progestin.

The net effect of these changes may be clinically relevant in some cases.

Therefore, the prescribing information of concomitant HIV/HCV medications should be consulted to identify potential interactions and any related recommendations. In case of any doubt, an additional barrier contraceptive method should be used for those women on protease inhibitor or non-nucleoside reverse transcriptase inhibitor therapy.

Substances decreasing the clearance of levonorgestrel (enzyme inhibitors)

Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. fluconazole, itraconazole, ketoconazole, voriconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concentrations of levonorgestrel. The clinical relevance of potential interactions with enzyme inhibitors remains unknown.

Effects of Norgeston on other medicinal products

Progestogens may affect the metabolism of certain other drugs. Accordingly, plasma and tissue concentrations may be increased (e.g. ciclosporin) or decreased (e.g. lamotrigine). Progestogens may either enhance or reduce the anticoagulant effects of coumarins and may antagonize the anticoagulant effects of phenindione.

Other forms of interaction

Effect on blood chemistry:
The use of oral contraceptives may influence the results of certain laboratory tests including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of carrier proteins and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Laboratory staff should therefore be informed about oral contraceptive use when laboratory tests are requested.

4.6 Fertility, pregnancy and lactation

The administration of Norgeston during pregnancy is contraindicated.

If pregnancy occurs during medication with Norgeston the preparation is to be withdrawn immediately.

Epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used oral contraceptives prior to pregnancy, nor a teratogenic effect when oral contraceptives were taken inadvertently during early pregnancy.

Hormonal contraceptives are not recommended as the contraceptive method of first choice during lactation, but progestogen-only methods are considered to comprise the next choice category after non-hormonal methods. Levonorgestrel passes into milk but the available data show no adverse effects on infant growth and development. Levels of levonorgestrel obtained with Norgeston do not affect the quantity or quality of breast milk. A breast-feeding woman can start a progestogen-only treatment, like Norgeston, up to 21 days post-partum without the need for additional contraceptive protection. When starting later, the woman should be advised to additionally use a barrier method for the first 7 days of tablet taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of Norgeston use or the woman has to wait for her first menstrual period.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Summary of the safety profile:

The most commonly reported adverse reactions with progestogen-only pills including Norgeston are uterine/vaginal bleeding including spotting, menorrhagia and/or metrorrhagia and amenorrhea. They occur in ≥ 10 % of users.

The undesirable effects are mapped to the respective System Organ Class (SOC), based on MedDRA v. 13.1. The SOCs are listed in the international order of MedDRA SOCs:

Immune system disorders
Allergic reaction

Metabolism and nutrition disorders
Increased or decreased weight

Psychiatric disorders
Depressed mood

Nervous system disorders
Migraine, Headache, Dizziness

Gastrointestinal disorders
Vomiting, Nausea

Reproductive system and breast disorders
Changes in vaginal bleeding pattern (including irregular bleeding, amenorrhoea)
Decreased or increased libido

The following serious adverse events have been reported in women using OCs, which are discussed in section 4.4 'Special warnings and precautions for use':

- Venous thromboembolic disorders
- Arterial thromboembolic disorders
- Strokes (e.g. transient ischemic attack, ischemic stroke, haemorrhagic stroke)
- Benign and malignant liver tumours leading in isolated cases to life-threatening intra-abdominal haemorrhage
- Diabetes mellitus or tendency towards diabetes mellitus require careful medical supervision.
- A history of ectopic pregnancy or a missing Fallopian tube require careful weighing of the benefits of Norgeston against the risks.

The frequency of breast cancer is very slightly increased among OC users. As breast cancer is rare in women under 40 years of age the excess number is small in relation to the overall risk of breast cancer. For progesterone-only pills (POPs) the evidence for causation is less conclusive than that for combined oral contraceptives (COCs).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There have been no reports of serious deleterious effects from overdose. Symptoms that may occur in this case are: nausea, vomiting and slight vaginal bleeding. There are no antidotes and further treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens, ATC code: G03AC03

Mechanism of action

The contraceptive action of Norgeston may be explained as follows: it changes the cervical mucus so that a barrier is formed against the migration of sperm into the uterine cavity; nidation is impeded because of changes in the structure of the endometrium. As a rule there is no inhibition of ovulation. Evidence suggests that a reduction in corpus luteum function may also contribute to the contraceptive action.

Clinical efficacy and safety

The pregnancy rate of progestogen-only pills (POPs) is slightly higher than that of other hormonal medicinal products for contraception. Combined oral contraceptives, when taken correctly, have a failure rate of approximately 1 % per year.

The contraceptive efficacy of Norgeston has been studied in a clinical trial with 1,645 women using Norgeston (27,939 treatment cycles in total). The uncorrected Pearl Index was 4.19 (95% CI: 3.37 – 5.15). For method failures only, a corrected Pearl Index of 1.0 was found. The efficacy of Norgeston is comparable to that of other POPs and the Pearl Index for Norgeston is similar to the range of 1.55-4.14 reported for POPs which do not completely inhibit ovulation. The failure rate of Norgeston may increase when pills are missed or taken incorrectly.

5.2 Pharmacokinetic properties

As is known from a series of studies comprising various preparations and dosages, levonorgestrel is rapidly and completely absorbed after oral administration. Following ingestion of Norgeston, maximum serum levels of about 0.8 ng/ml were determined at 1 hour. Thereafter, drug serum levels declined biphasically with half-lives of 0.2 - 0.4 hours and 20 hours. Metabolic clearance rate from serum or plasma accounts for 1.0 to 1.5 ml/min/kg. Levonorgestrel is not excreted in unchanged form but as metabolites, which are eliminated with a half-life of about 1 day. Almost equal dose parts are excreted via the kidney and the liver. The biotransformation follows the known pathways of steroid metabolism. No pharmacologically active metabolites are known.

Levonorgestrel is bound to serum albumin and to SHBG. Only about 1.5% of the respective total serum drug levels are present as free steroid, but about 65% are specifically bound to SHBG. The relative portions (free, albumin-bound, SHBG-bound) depend on the SHBG serum concentrations. Following induction of the carrier protein, the SHBG-bound portion increases while the unbound and albumin-bound portions decrease.

Following daily repeated administration, levonorgestrel accumulates by a factor of approx. 2. Steady-state conditions are reached after about 3 - 4 days. Levonorgestrel pharmacokinetics is influenced by SHBG serum levels.

Under Norgeston treatment, a slight decline of the SHBG serum levels could occur. The daily ingestion of 0.15 mg levonorgestrel (corresponding to the 5 fold daily dose of Norgeston) led to a 50% decrease in the SHBG serum levels and thus to a 40% reduction in levonorgestrel through levels after 2 - 3 weeks. A similarly directed effect of Norgeston should account, however, for a decrease of only about 10% in the two parameters. The absolute bioavailability of levonorgestrel from Norgeston was determined to 82% of the dose. About 0.1% of the maternal dose can be transferred to a newborn via milk.

Special populations

Serum levonorgestrel (LNG) concentrations decrease with increasing body weight. According to a population pharmacokinetic analysis, average LNG concentrations decreased from a range of approximately 288 to 379 ng/L for a body weight of 55 kg to LNG concentrations between 196 and 264 ng/L for a body weight of 80 kg, depending on baseline SHBG (for a range of 50 to 100 nmol/L). For women with higher body weight, LNG average concentrations decrease even further; the difference in LNG concentration between women weighing 45 kg or 90 kg is about two-fold. In the absence of relevant data, the effect of decreased LNG serum concentrations on the contraceptive efficacy is currently not quantifiable.

Biotransformation

Levonorgestrel (LNG) is extensively metabolized. The most important metabolic pathways are the reduction of the Δ4-3-oxo group and hydroxylations at positions 2α, 1β and 16β,

followed by conjugation. CYP3A4 is the main enzyme involved in the oxidative metabolism of LNG. The available in vitro data suggest that CYP mediated biotransformation reactions may be of minor relevance for LNG compared to reduction and conjugation.

5.3 Preclinical safety data

Non-clinical data reveal no special risk for humans based on studies of repeated dose toxicity, genotoxicity, carcinogenicity and toxicity to reproduction which is not already included in other relevant sections. However, it should be kept in mind that sexual steroids might stimulate the growth of hormone-dependent tissues and tumours.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Maize starch
Povidone
Talc
Magnesium stearate [E572]
Sucrose
Polyethylene glycol 6000
Calcium carbonate [E170]
Montan glycol wax

6.2 Incompatibilities

None known

6.3 Shelf life

5 years

6.4 Special precautions for storage

Not applicable.

6.5 Nature and contents of container

Norgeston tablets are contained in aluminium foil and PVC blister packs.

These calendar-packs contain 35 tablets

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Bayer plc
400 South Oak Way
Reading
RG2 6AD

8 MARKETING AUTHORISATION NUMBER(S)

PL 00010/0550

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02/12/2008

10 DATE OF REVISION OF THE TEXT

29/01/2021