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APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

DUPHASTON 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg dydrogesterone.

Excipient with known effect:

Contains sugar: Each tablet contains 111,1 mg lactose monohydrate.

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

A round, biconvex, scored white film-coated tablet, one side with inscription '155' on either side of the score. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Irregular duration of cycles and irregular occurrence and duration of periods caused by progesterone deficiency.
- Endometriosis.
- Dysmenorrhoea.
- Infertility as a result of corpus luteum insufficiency.
- Luteal support as part of an Assisted Reproductive Technology (ART) treatment.
- Threatened miscarriage as a result of progesterone deficiency.
- Habitual miscarriage as a result of progesterone deficiency.

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As a cyclical supplement to oestrogen therapy in women with an intact uterus, DUPHASTON can be used:

- to prevent endometrial hyperplasia in the postmenopausal period
- for dysfunctional uterine bleeding
- for secondary amenorrhoea.

4.2 Posology and method of administration

Posology

The following dosage regimens are recommended for treatment with DUPHASTON. The quantities can be adjusted according to the seriousness of the disorder to be treated and the individual patients' responses to the treatment.

Regulation of the cycle

It is possible to achieve a cycle lasting 28 days by giving 1 tablet (10 mg) of DUPHASTON a day from the 11th to the 25th day of the cycle.

Endometriosis

1 to 3 tablets of DUPHASTON a day from the 5th to the 25th day of the cycle.

Dosages of 10 mg several times a day should be spread over the day. It is recommended to start treatment with the highest dosage.

Dysmenorrhoea

1 to 2 tablets of DUPHASTON a day from the 5th to the 25th day of the cycle. Dosages of 10 mg several times a day should be spread over the day. It is recommended to start the treatment with the highest dosage.

Infertility as a result of corpus luteum insufficiency

1 tablet of DUPHASTON a day from the 14th to the 25th day of the cycle.

Treatment should be continued for at least 3 consecutive cycles. It is advisable to continue this treatment for the first months of any pregnancy at dosages as indicated for habitual miscarriage.

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Luteal support as part of an Assisted Reproductive Technology (ART) treatment

1 tablet of DUPHASTON three times a day (30 mg daily) starting at the day of oocyte retrieval and continuing for 10 weeks if pregnancy is confirmed.

Threatened miscarriage

Starting dose: 4 tablets of DUPHASTON at once followed by 1 tablet of DUPHASTON every 8 hours. Dosages of 10 mg several times a day should be spread over the day. It is recommended that treatment should start at the highest dose.

If the symptoms persist or recur during the treatment, the dose should be increased by 1 tablet of DUPHASTON every 8 hours.

The effective dose should be maintained for one week after symptoms have ceased; it can then be gradually reduced. If the symptoms recur, the treatment should be resumed immediately at the effective dose.

Habitual miscarriage

1 tablet of DUPHASTON twice daily up to the 12th week of pregnancy; the dose can then be gradually reduced. Treatment should preferably be started before conception.

If the symptoms of threatened miscarriage occur during treatment, treatment should be continued as described for that indication.

Dysfunctional uterine bleeding

Bleeding is stopped by 2 tablets of DUPHASTON a day for 5 to 7 days. The blood loss is reduced considerably within a few days. A few days after the end of this treatment, a heavy withdrawal bleed occurs and the patient should be warned about this.

Subsequent heavy bleeding can be prevented by prescribing a prophylactic dose of 1 tablet of DUPHASTON a day from the 11th to the 25th day of the cycle, if necessary combined with an oestrogen for 2 to 3 cycles. After this the treatment can be discontinued, in order to check that the patient has a normal cycle again.

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Secondary amenorrhoea

1 or 2 tablets of DUPHASTON per day from the 11th to the 25th day of the cycle to give optimum secretion transformation of the endometrium, that is adequately prepared with an endogenous or exogenous oestrogen.

Prevention of hyperplasia of the endometrium in the post menopause

If on continuous sequential oestrogen therapy:

For each cycle of 28 days oestrogen therapy for the first 14 days oestrogen only is used and for the following 14 days in addition to oestrogen therapy once a day 1 or 2 tablets of dydrogesterone 10 mg are taken. With a dose of 2 tablets of dydrogesterone 10 mg per day the tablets must be taken in divided doses over the day. Withdrawal bleeding usually occurs while taking dydrogesterone.

If on cyclic oestrogen therapy:

When an estrogen is dosed cyclically with a treatment-free interval, usually 21 days on and 7 days off. One or two tablets of 10 mg dydrogesterone is added for the last 12 – 14 days of estrogen therapy.

Use of combined oestrogen/progesterone therapy in postmenopausal women should be limited to the lowest effective dose and the shortest time compatible with the treatment aims and risks for the individual woman and must be regularly assessed (see section 4.4).

Method of administration

For oral use.

For administration of higher doses, the tablets should be taken evenly distributed over the day.

Paediatric population

There is no relevant use of dydrogesterone before the menarche. The safety and efficacy of DUPHASTON in adolescents 18 years and younger has not been established.

4.3 Contraindications

- Hypersensitivity to dydrogesterone or to any of the excipients listed in section 6.1.

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- Vaginal bleeding where the cause has not been established or a history of thromboembolic disorders.
- Known or suspected progestogen dependent neoplasms.
- If used to prevent endometrial hyperplasia (in women using estrogens):

  Contraindications for use of oestrogens in combination with progestogens, such as dydrogesterone.
- Personal and family history of breast cancer
- Previous proven deep-vein thrombosis (DVT)
- Previous pulmonary embolism
- Inherited thrombophilia
- Active liver disease
- Patients known with inherited genetic mutations: BRCA1 and BRCA 2 genes
- Early menstrual periods (before the age of 12 years)
- History of non-cancerous breast diseases (atypical hyperplasia or lobular carcinoma in situ)
- Previous treatment using radiation therapy to the chest or breast
- Previous exposure to diethylstilbestrol (DES)

4.4 Special warnings and precautions for use

DUPHASTON should be used with caution in patients with cardiovascular, renal or hepatic impairment, diabetes mellitus, asthma, epilepsy and migraine. It should be used with care in persons with a history of mental depression.

Before initiating treatment with DUPHASTON because of dysfunctional uterine bleeding an organic cause should be excluded.

Breakthrough bleeding and spotting may occur during the first months of treatment. If breakthrough bleeding and spotting continues once treatment has already been initiated, or continue when treatment is discontinued, the cause should be ascertained, if necessary, by taking an endometrial biopsy to exclude malignancy of the endometrium.

Treatment for luteal support as part of an Assisted Reproductive Technology (ART) treatment should be discontinued upon diagnosis of abortion or miscarriage.

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If one of the following disorders occurs during use for the first time or gets worse, treatment should be stopped.

- exceptionally severe headache, migraine or symptoms that may indicate cerebral ischemia.
- marked increase in blood pressure.
- occurrence of venous thromboembolism.

In cases of threatened or habitual miscarriage, the viability of the foetus should be ascertained, and it is necessary to monitor the progress of the pregnancy and whether the embryo is still alive.

Treatment with DUPHASTON has been associated with alterations in liver function, sometimes accompanied by clinical symptoms. Thus, DUPHASTON should be used with caution in patients with acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal. In cases of severe hepatic impairment treatment should be discontinued (see also section 4.3).

Conditions for which monitoring is necessary:

If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with DUPHASTON, in particular:

- Porphyria,
- cholestatic icterus,
- herpes gestationis,
- severe pruritus,
- otosclerosis,
- Depression.

Patients with a history of depression must be carefully monitored; if severe depression recurs, treatment with DUPHASTON must be stopped.

Other conditions:

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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Warnings and precautions when using DUPHASTON in the indication "To prevent endometrial hyperplasia in the postmenopausal period:

NB: See also the warnings in the product information of the oestrogen preparation.

To treat post-menopausal symptoms, treatment with hormone replacement therapy (HRT) must only be started if these symptoms adversely affect the quality of life. Periodically, at least annually, a careful assessment of the advantages and disadvantages of HRT must be carried out and the treatment must only be continued if the advantages outweigh the disadvantages.

Medical examination / follow-up:

- Before starting hormone replacement therapy (HRT) or when its use is resumed after an interruption a full medical history (including family medical history) must be taken. A physical examination (including gynaecological and breast examination) must be carried out as guided by the history, the contraindications and the warnings. During the treatment period regular checkups are recommended, the frequency and nature of which are adapted to the individual. Women must be told what changes in their breasts they must report to their doctor (see "Breast cancer" below).
- Regular examination of the breasts, including a mammography, must be carried out in accordance with the current guidelines for healthy women, taking into account here the medical need of the individual woman.

Endometrial hyperplasia and carcinoma:

- Long-term use of oestrogens without addition of progestagens increases the chance of endometrial hyperplasia and endometrial carcinoma in women with a uterus. Depending on the duration and oestrogen dose the risk may be 2 to 12 times higher than in women who do not use oestrogen. After stopping oestrogen treatment this risk continues to exist for at least 10 years. This risk may largely be prevented by combining the oestrogen therapy for at least 12 days per month/28 day cycle with a progestagen, such as dydrogesterone.
- Breakthrough bleeding and spotting may occur during the first months of treatment. If breakthrough bleeding or spotting occur after considerable time on treatment or continue when treatment is

discontinued, further investigation is indicated. This may mean taking an endometrial biopsy to exclude malignancy.

Breast cancer:

- All the available data indicate an increased risk of breast cancer if women take a combination of oestrogen and progestogen as HRT and possibly even if they take oestrogen-only as HRT. This risk depends on the duration of use.
- DUPHASTON contains (oestrogen and progestogen or oestrogen only) which, on prolonged use, may increase the risk of developing breast cancer. A meta-analysis of prospective epidemiological studies from 1992 to 2018 reported a significant increase in the risk of developing breast cancer in 55,575 women 40 – 59 years of age who used menopausal hormone therapy (MHT).
- The risk increased steadily with duration of use and was slightly greater for oestrogen-progestogen than oestrogen only preparations, and the risk persisted for more than 10 years after stopping the treatment. The relative risk (RR) to develop breast cancer for oestrogen-progestogen preparations was 1.60 at 1-4 years and RR=2.08 at 5-14 years, while that for oestrogen only preparations was 1.17 at 1-4 years and 1.33 at 5-14 years. There was no risk of to develop breast cancer in women who started MHT at 60 years of age.
- All women on DUPHASTON should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. Mammography evaluations should be done based on patient age, risk factors, and prior mammogram results.

Combined treatment with oestrogen and progestogen:

- A randomised placebo-controlled study, the Women's Health Initiative Study (WHI) and epidemiological studies, including the Million Women Study (MWS) have shown that in women who have taken oestrogen, oestrogen-progestogen combinations or tibolone as hormone replacement therapy for a number of years there is a relative increased risk of breast cancer. For all HRT this increased risk occurs within a couple of years of use and increases as the treatment period continues. The risk returns within a couple of years (a maximum of 5) after the treatment is discontinued to the level before the treatment.

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The MWS showed that the relative risk of breast cancer in women who were treated with conjugated equine oestrogens (CEE) or oestradiol (E2) was higher when a progestogen was added. This risk was independent of the dosage schedule used (sequential or continuous administration of progestogen) and the type of progestogen.

Ovarian cancer

- Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking oestrogen-only or combined oestrogen-progestogen HRT, which becomes apparent within 5 years of use and diminishes over time after stopping. Some other studies, including the WHI trial, suggest that use of combined HRTs may be associated with a similar, or slightly smaller risk (see section 4.8).
- If any progestogen dependent neoplasms e.g. meningioma have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patients should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with DUPHASTON.

Venous thrombo-embolism:

- Hormone replacement therapy is associated with a 1,3 – 3 times higher relative risk of the occurrence of a venous thromboembolism (VTE), that is deep vein thrombosis or pulmonary embolism. One randomised controlled study and epidemiological studies report 2 – 3 times higher risk of VTE among users of HRT compared with women who do not use HRT. The chance of this is greater during the first year of HRT treatment than thereafter.
- Generally recognised risk factors for the occurrence of VTE are a positive personal history, a positive family history, the use of oestrogens, greater age, major surgery, long-term immobilisation, obesity (BMI > 30 kg/m^2), pregnancy/postpartum period, systemic lupus erythematosus (SLE) and cancer. There is no consensus regarding the possible role of varicose veins in the occurrence of VTE.
- Patients with a previous history of repeated VTE or known thrombophilia have an increased chance of developing VTE and HRT could increase this risk even further. In the presence of a previous personal or clear family history of VTE or repeated spontaneous abortion an investigation must first be carried out to exclude a thrombophilic predisposition. Until a thorough evaluation of the thrombophilic factors

have been carried out or anticoagulant therapy has been started, the use of HRT in these patients is contra-indicated. In women who are already being treated with anticoagulant therapy, a careful assessment of the advantages and disadvantages of the treatment must be made.

- The chance of VTE may have increased temporarily during long-term immobilisation, serious trauma or major surgical operation. As in all postoperative patients careful attention must be paid to prophylactic measures to prevent VTE after surgery. If after elective surgery (in particular abdominal or orthopaedic surgery of the lower limbs) long-term immobilisation is anticipated, consideration must be given to interrupting the HRT 4 – 6 weeks before the operation and only resuming it when the woman is fully mobilized again.
- Women who themselves have no history of VTE but who have a first degree relative who has had thrombosis at a young age can be offered screening after the limitations of this have been clearly discussed (only a certain number of thrombophilic abnormalities can be determined by screening). If a thrombophilic deviation is found which has led to thrombosis in family members or if it relates to a serious abnormality (e.g. antithrombin, protein S or protein C deficiency, or a combination of defects) HRT is contraindicated.
- In women who are already receiving anticoagulant therapy, the benefits and risks of HRT should be carefully assessed.
- If a VTE develops after starting the therapy, the administration of the medication must be discontinued. Patients must be informed that they should contact their doctor immediately if potential thrombo-embolic

  symptoms occur (for example: painful swelling of a leg, sudden pain in the chest, shortness of breath).

Coronary heart disease (CHD):

- Randomised controlled studies have produced no evidence that women with or without existing CHD who received HRT with oestrogen in combination with progestogen or oestrogen-only were protected against myocardial infarction. Two large clinical studies (WHI and HERS (Heart and Estrogen/progestin Replacement Study)) showed a possible increased risk of cardiovascular morbidity during the first year of use and no indications of an overall favourable effect.

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Combined treatment with oestrogen and progestogen:

- The relative risk of the occurrence of CHD during HRT with a combination of oestrogen and progestogen is slightly increased. Since the baseline absolute risk of the occurrence of CHD is greatly dependent on age, the number of extra cases of CHD as a result of the use of oestrogen-progestogen in women approaching menopause is very low, but that does increase as they get older.

Cerebrovascular accident (CVA):

- In one large randomised clinical trial (WHI study) in healthy women, as a secondary outcome, an increased risk of ischaemic CVA was reported during treatment with continuous combined conjugated oestrogens with medroxyprogesterone acetate.

  Use of combined HRT or HRT with oestrogen-only is accompanied by a 1 to 1,5 times higher risk of ischaemic CVA. The relative risk does not change with ageing or with the time that has elapsed since the menopause. However, because the basic risk of CVA is highly dependent on age, the absolute risk will increase with ageing.

DUPHASTON contains lactose

- Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take DUPHASTON.

4.5 Interaction with other medicines and other forms of interaction

In vitro data indicate that the main active metabolite 20α-dihydrodydrogesterone (DHD) and to less extent also dydrogesterone are primarily metabolized by CYP3A4.

Substances that increase the clearance of progestogens (less efficacy due to enzyme induction) are for example: barbiturates, phenytoin, carbamazepine, primidone, rifampicin and HIV medication like ritonavir, neviparine and efavirenz, and possibly also products containing the herb St. John's Worth (hypericum perforatum).

An increase in the clearance of dydrogesterone may lead to a clinical decrease of effect and changes in the bleeding pattern.

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Substances with variable effects on the clearance of progestogens:

Many combinations of HIV protease inhibitors and non-nucleoside reverse-transcriptase inhibitors, including combinations with HCV inhibitors could, if concomitantly administered with progestogens, raise or lower the plasma concentrations of the progestogen. In some cases the net effect of these changes could be clinically relevant.

For this reason the product information of HIV/HCV medicines should be consulted, if they are administered concomitantly, to determine potential interactions and any associated recommendations.

Substances that decrease clearance of progestogens (enzyme inhibitors):

The clinical relevance of possible interactions with enzyme inhibitors is unknown. Concomitant use of strong CYP3A4 inhibitors may raise the plasma concentrations of progestogens.

4.6 Fertility, pregnancy and lactation

Pregnancy

It is estimated that over 9 million women have already been exposed to dydrogesterone during pregnancy. To date there were no indications that the use of dydrogesterone during pregnancy has a harmful effect. In the literature a study is described in which it was found that the use of some progestogens can be accompanied by an increase in the risk of hypospadias occurring. However, because this has not been clearly confirmed to date in other studies, no final conclusion can be drawn about the effect of progestogens on the occurrence of hypospadias.

Clinical trials in which a limited number of women were treated with dydrogesterone in the first stage of pregnancy did not show that the risk is increased. To date no other epidemiological data are available.

The effects that were observed during non-clinical study into embryo-foetal and postnatal development corresponded with the pharmacological profile. Unwanted effects only occurred in case of exposure that was considerably higher than the maximum exposure in humans (see section 5.3).

Breastfeeding

It is not known whether DUPHASTON is excreted in breast milk. No research has been done into the

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excretion of dydrogesterone in breast milk. Experiences with other progestogens indicate that progestogens and their metabolites are found in small quantities in breast milk. It is not known whether there is a risk for the child. DUPHASTON should therefore not be used while breastfeeding.

Fertility

There are no data on the effect of DUPHASTON on fertility.

4.7 Effects on ability to drive and use machines

DUPHASTON may cause somnolence and/or dizziness, in particular during the first couple of hours after taking it. Caution is therefore advised when driving and operating machinery.

4.8 Undesirable effects

The most commonly reported side-effects of patients treated with dydrogesterone in clinical trials of indications without oestrogen treatment are vaginal haemorrhage, metrorrhagia, breast pain/tenderness, nausea, vomiting, abdominal pain and migraines/headache.

The following undesirable effects, with the frequencies indicated, were observed during clinical trials with dydrogesterone (n=3 483) for indications without oestrogen treatment in two company sponsored interventional clinical trials in luteal support as part of an ART treatment using dydrogesterone (n = 1 036) and from spontaneous reporting. Frequencies are based on the most conservative approach.

MedDRA system organ class	Very common ≥1/10	Common ≥1/100, < 1/10	Uncommon ≥1/1,000, < 1/100	Rare ≥1/10,000, < 1/1,000
Immune system disorders				Hypersensitivity
Psychiatric disorders			Depressed mood	
Nervous		Migraines/	Dizziness	Somnolence

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system disorders		headache		
Gastrointestinal disorders		Nausea, vomiting, abdominal pain		
Hepatobiliary disorders			Abnormal hepatic function (with Jaundice, Asthenia or Malaise, and Abdominal pain)	
Skin and subcutaneous tissue disorders			Allergic skin reactions (e.g. rash, pruritis, urticaria)	
Reproductive system and breast disorders	Vaginal haemorrhage	Disturbed menstruation (including metrorrhagia, menorrhagia, oligo-/amenorrhoea, dysmenorrhoea and irregular menstruation) Breast pain/tenderness		Breast swelling
General disorders and administration			Oedema	

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site conditions				
Investigations			Increased weight	

Other adverse reactions obtained from post marketing with unknown frequency in association with dydrogesterone treatment:

- **Benign, malignant and unspecified neoplasms (including cysts and polyps):**
- Increase in size of progestogen dependent neoplasms (e.g. meningioma) (see section 4.3);
- **Blood and lymphatic system disorders:**
- Haemolytic anaemia;
- **Skin and subcutaneous tissue disorders:**
- Angioedema.

Undesirable effects that are associated with an oestrogen-progestogen treatment (see section 4.4)

- Breast cancer;
- Endometrial hyperplasia, endometrial carcinoma; ovarian cancer;
- Ovarian cancer: use of oestrogen-only or combined oestrogen-progestogen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see section 4.4). A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using HRT compared to women who have never used HRT (RR 1,43, 95 % CI 1,31 – 1,56).
  For women aged 50 to 54 years taking 5 years of HRT, this results in about 1 extra case per 2 000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2 000 will be diagnosed with ovarian cancer over a 5-year period.
- Sex hormone dependent tumours (malignant/benign);
- Venous thrombo-embolism;
- Myocardial infarction, coronary heart disease, ischemic cardiovascular accident.

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. Health care providers are asked

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to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms

Limited data are available with regard to overdose in humans. Dydrogesterone is a substance with very low toxicity. Nausea, vomiting, lethargy and dizziness are symptoms which may theoretically occur in the event of an overdose.

Treatment

There are no specific antidotes and treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A.21.8.2 Progesterones without estrogens.

Pharmacotherapeutic category: Urogenital system and sex hormones, pregnadien derivatives

ATC code: G03DB01

Mechanism of action

Dydrogesterone is a synthetic progesterone with an oral biological availability that causes a secretory phase of the endometrium in a uterus prepared by oestrogen.

Dydrogesterone has no oestrogenic, androgenic, anabolic and corticoid properties.

At therapeutic levels, dydrogesterone has no contraceptive effect as it does not inhibit or interfere with ovulation or the corpus luteum. As a result, conception remains possible if dydrogesterone is used by women of child-bearing age.

In postmenopausal women with a uterus, oestrogen replacement leads to an increase in the risk of endometrial hyperplasia and endometrial carcinoma. The addition of a progestogen prevents this additional risk.

5.2 Pharmacokinetic properties

Absorption

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The T_{max} values of dydrogesterone and DHD are about 1.5 hours.

The absolute biological availability of dydrogesterone (20 mg oral dose versus 7,8 mg intravenous infusion) is 28 %.

The main metabolite of dydrogesterone is 20α-dihydrodydrogesterone (DHD).

Distribution

After intravenous administration of dydrogesterone the steady-state distribution volume is around 1 400 L. More than 90 % of dydrogesterone and DHD are bound to plasma-proteins.

Metabolism

After oral administration dydrogesterone is metabolized quickly to DHD. *In vitro* data show that the main route of metabolism, the one that generates DHD, is catalyzed in human cytosol by aldo-keto reductase 1C (AKR 1C). Other metabolic routes by cytochrome P450 iso enzymes (CYPs) exist, this is nearly exclusively CYP 3A4, in which less important metabolites are formed. The concentration of the main active metabolite DHD shows a peak concentration approximately 1,5 hours after administration. The plasma concentrations of DHD are substantially higher than the related drug. The AUC and C_{max} ratios of DHD and dydrogesterone are approximately 40 and 25. The mean terminal half-lives of dydrogesterone and DHD vary between 5 – 7 and 14 – 17 hours, respectively. A common feature of all characterized metabolites is the maintenance of the 4,6-diene-3-on configuration of the initial drug and the missing 17a-hydroxylation. This clarifies the lack of estrogen and androgen effects of dydrogesterone.

Elimination

After oral administration of labelled dydrogesterone on average 63 % of the dose is excreted in the urine. The total plasma clearance is 6,4 L/minute. Within 72 hours excretion is complete DHD is present in the urine, predominantly as the conjugated glucuronic acid.

Dependence of dose and time

The pharmacokinetics of single and multiple doses are linear in the oral dosage range from 2,5 to 10 mg. Comparison of the kinetics of single and multiple doses shows that the pharmacokinetics of dydrogesterone

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and DHD do not change as a result of repeated dosing. Steady state is reached after 3 days of treatment.

5.3 Preclinical safety data

Non-clinical data obtained during conventional investigation into the toxicity of single and repeated doses, genotoxicity and the carcinogenic potential do not show any special risks for humans.

Research into the toxic effects on the reproduction of rats shows for high doses (> 80 times the human exposure) an increased incidence of erect nipples (during days 11 – 19 of the lactation period) and of hypospadia in male rats. The clinical relevance of these observations is not known.

The limited data on safety in animals indicate that dydrogesterone has an extending effect on delivery, which corresponds with the progestogenic action.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Composition of the tablet:

Hypromellose

Lactose monohydrate

Magnesium stearate

Maize starch

Silicon dioxide

Composition of the coating:

Hypromellose

Macrogol 400

Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

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6.4 Special precautions for storage

Store in a dry, dark place at temperatures not exceeding 25 °C.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Clear PVC/aluminium blister strips placed in an outer carton.

Available in packs of 30 tablets.

6.6 Special precautions for disposal and other handling

Not applicable.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Abbott Laboratories S.A. (Pty) Limited

Abbott Place, 219 Golf Club Terrace

Constantia Kloof 1709

South Africa

8. REGISTRATION NUMBER

S/21.8.2/165

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 January 1993

10. DATE OF REVISION OF THE TEXT

8 August 2023