1. NAME OF THE MEDICINAL PRODUCT

Progyluton

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each white coated tablet contains estradiol valerate 2.0 mg.
Each light brown coated tablet contains estradiol valerate 2.0 mg and norgestrel 0.5 mg.

3. PHARMACEUTICAL FORM

Coated tablet

4. CLINICAL PARTICULARS

4.1 Indications

Hormone replacement therapy (HRT) for the treatment of signs and symptoms of estrogen deficiency due to menopause or hypogonadism, castration or primary ovarian failure in women with an intact uterus.

Prevention of postmenopausal osteoporosis.

Control of irregular menstrual cycles.

Treatment of primary or secondary amenorrhea.

4.2 Dosage and method of administration

4.2.1 Method of administration

Oral use.

4.2.2 Dosage regimen

Hormonal contraception should be stopped when HRT is started and the patient should be advised to take non-hormonal contraceptive precautions, if required.

- **How to start Progyluton**

If the patient is still menstruating, treatment should begin on the 5th day of the cycle (1st day of menstrual bleeding = 1st day of the cycle).

Patients with amenorrhea or very infrequent periods or who are post-menopausal may start at any time, provided pregnancy has been excluded (see section 4.6, “Pregnancy and lactation”).

- Dosage

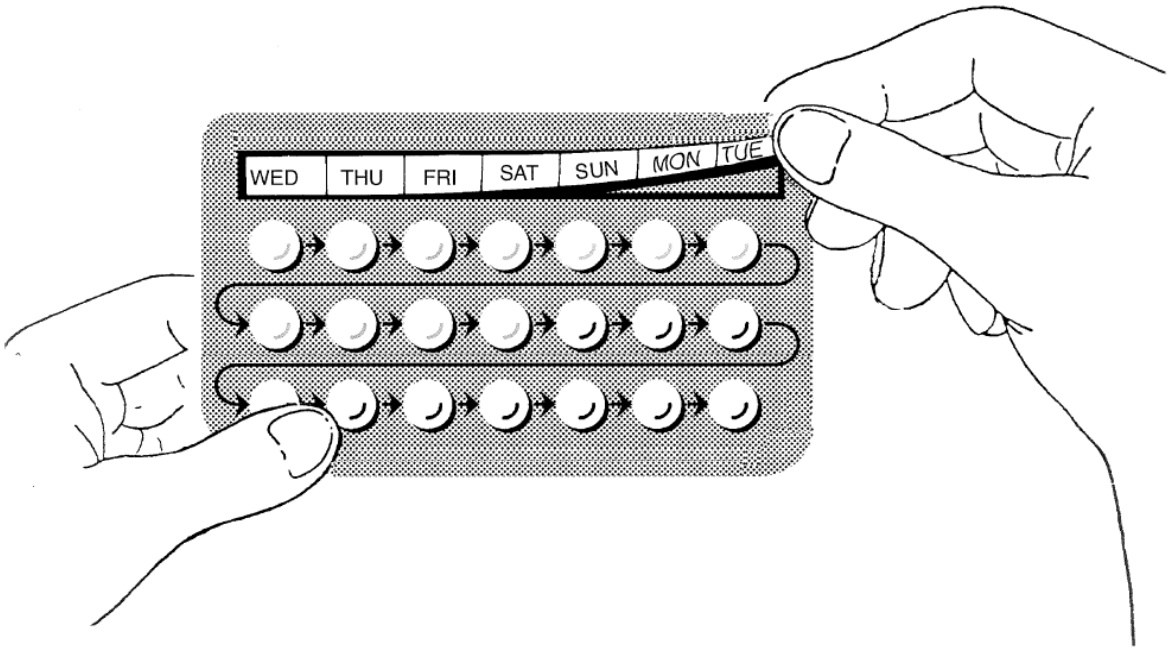
One white tablet is taken daily for the first 11 days, followed by one light brown tablet daily for 10 days. Following the 21 days of tablet-taking there will be a tablet-free interval of 7 days.

- Administration

Each pack covers 21 days of treatment. A new pack of Progyluton should be started after the 7-day tablet-free interval on the same day of the week as the previous one. The tablets are to be swallowed whole with some liquid. The tablets should preferably be taken at the same time every day.

Estrogen with or without progestogens should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual women.

The Progyluton pack contains a self-adhesive sticker marked with the days of the week. Choose the strip that starts with the day the patient begin tablet taking. For example, if the patient starts the tablets on a Wednesday, use the strip that starts with “Wed”. The strip should be stuck along the top of the blister-pack on the side, where the tablets are visible, so that the first day is above the first tablet of the row (see Figure). Each tablet is thus marked with the corresponding day of the week and one can see at a glance whether the tablet for that day has been taken or not. Follow the direction of the arrows from left to right until all 21 tablets have been taken. It does not matter at what time of the day the patient takes her tablet, but once she has selected a particular time, she should keep to it every day. If she forgets to take a tablet at the usual time she may take it within the following 12 to 24 hours. If the treatment is discontinued for longer, irregular bleeding may occur.



Bleeding usually occurs during the tablet-free interval of 7 days a few days after the last tablet was taken.

- Missed tablets

In case a tablet is forgotten, it should be taken as soon as possible. If more than 24 hours have elapsed, no extra tablet needs to be taken. If several tablets are forgotten, bleeding may occur. Bleeding usually occurs during the tablet-free interval of 7 days within a few days after the last tablet was taken.

4.2.3 Additional information on special populations

4.2.3.1 Pediatric patients
Progyluton is not indicated for use in children and adolescents.

4.2.3.2 Geriatric patients
There are no data suggesting a need for dosage adjustment in elderly patients.

4.2.3.3 Patients with hepatic impairment
Progyluton has not been specifically studied in patients with hepatic impairment. Progyluton is

contraindicated in women with presence or history of liver tumors and with severe hepatic disease (see section , “Contraindications”). For women with impaired liver function, close supervision is needed and in case of deterioration of markers of liver function, use of HRT should be stopped (see section ‘Special warnings and precautions for use’).

4.3.3.4 Patients with renal impairment
Progyluton has not been specifically studied in renally impaired patients.
Estrogen may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed.

4.3 Contraindication

Hormone replacement therapy (HRT) should not be started in the presence of any of the conditions listed below. Should any of the conditions appear during HRT use, the product should be stopped immediately.

- Pregnancy and lactation
- Undiagnosed vaginal bleeding
- Known or suspected cancer of the breast
- Known or suspected premalignant conditions or malignancies, if sex steroid-influenced
- Presence or history of liver tumours (benign or malignant)
- Severe hepatic disease
- Acute arterial thromboembolism (e.g. myocardial infarction, stroke)
- Active deep venous thrombosis, thromboembolic disorders, or a documented history of these conditions
- A high risk of venous or arterial thrombosis
- Severe hypertriglyceridemia
- Known hypersensitivity to any of the components of Progyluton

4.4 Special warnings and special precautions for use

Progyluton cannot be used as a contraceptive.

Where applicable, contraception should be practised with non-hormonal methods (with the exception of the rhythm and temperature methods). If there is a chance that pregnancy has occurred, tablet-taking must be interrupted until it has been ruled out (see section “Pregnancy and lactation”).

Before initiating therapy, all conditions/risk factors mentioned below should be considered when determining the individual benefit/risk of treatment for the patient.

During HRT use, therapy should be discontinued immediately in case a contraindication is discovered, as well as in the following situations:

- Migrainous or frequent and unusually severe headaches that occur for the first time or other symptoms that are possible prodroma of cerebrovascular occlusion.
- Recurrence of cholestatic jaundice or cholestatic pruritus which occurred first during pregnancy or previous use of sex steroids.
- Symptoms of thrombotic event or suspicion thereof.

In the event of new onset or deterioration of the following conditions or risk factors, the individual benefit/risk analysis should be re-done, taking into consideration the possible necessity of discontinuing therapy.

The potential for an increase synergistic risk of thrombosis should be considered in women who possess a combination of risk factors or exhibit a greater severity of an individual risk factor. This

increased risk may be greater than a simple cumulative risk of the factors. HRT should not be prescribed in case of a negative risk-benefit assessment.

HRT should not be initiated or continued to prevent coronary heart disease and the benefits and risks of HRT must be carefully weighed when considering use in women without menopausal symptoms or for long-term use.

When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and for whom non-estrogen medications are not considered to be appropriate. Other non-HRT treatments should be considered prior to initiation of HRT.

The WHI study recruited 16,608 postmenopausal women in the USA. Participants received conjugated equine estrogens, 0.625mg/day, plus medroxyprogesterone acetate 2.5mg/day, in 1 tablet (marketed in the USA as Prempro), or placebo. The 8-year study was designed primarily to assess whether long-term use of this combined HRT preparation reduces the risk of coronary heart disease (CHD) in postmenopausal women. It was stopped early (after an average of 5.2 years) as the overall health risks of the combined HRT preparation exceeded the benefits of the drug.

The results of the study suggest that for every 10,000 women treated with the HRT preparation, an extra 7 women developed heart disease, an extra 8 had a stroke, an extra 8 had a serious blood clot in the lungs and extra 8 developed breast cancer. In contrast, 6 fewer women developed colorectal cancer and 5 fewer suffered a hip fracture. The WHI study, which was published in the 17 July edition of JAMA, reported that the absolute excess risks per 10,000 person years attributable to estrogen plus progestin were 7 more CHD events, 8 more strokes, 8 more pulmonary embolisms, and 8 more invasive breast cancers, while absolute risk reductions per 10,000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The study concluded that overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2 year follow-up among healthy postmenopausal US women. All-cause mortality was not affected during the trial. The risk-benefit profile found in the trial is not consistent with the requirements for a viable intervention for primary prevention of chronic diseases, and the results indicate that the regimen should not be initiated or continued for primary prevention of CHD.

- Venous thromboembolism

Both randomized-controlled and epidemiological studies have suggested that hormone replacement therapy (HRT) may be associated with an increased relative risk (RR) of developing venous thromboembolism (VTE), i.e. deep venous thrombosis or pulmonary embolism**.** Risk/benefit should therefore be carefully weighed in consultation with the patient when prescribing HRT to women with a risk factor for VTE.

Generally recognized risk factors for VTE include a personal history, a family history (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic disposition) and severe obesity. The risk of VTE also increases with age. There is no consensus about the possible role of varicose veins in VTE.

The risk of VTE may be temporarily increased with prolonged immobilization, major elective or post-traumatic surgery, or major trauma. Depending on the nature of the event and the duration of the immobilization, consideration should be given to a temporary discontinuation of HRT.

- Arterial thromboembolism

Two large clinical trials with continuous combined conjugated estrogens (CEE) and medroxyprogesterone acetate (MPA) showed a possible increased risk of coronary heart disease (CHD) in the first year of use and no benefit thereafter.

One large clinical trial with CEE alone showed a potential reduction of CHD rates in women aged 50-59

and no overall benefit in the total study population.

As a secondary outcome, in two large clinical trials with CEE alone or combined with MPA, a 30-40% increased risk of stroke was found.

It is uncertain whether these findings also extend to other HRT products or non-oral routes of administration.

•Gallbladder disease
Estrogens are known to increase the lithogenicity of the bile. Some women are predisposed to gallbladder disease during estrogen therapy.

•Dementia
There is limited evidence from clinical studies with CEE-containing preparations that hormonal treatment may increase the risk of probable dementia if initiated in women aged 65 or older. It is unknown whether these findings apply to younger postmenopausal women. It is unknown whether these findings also extend to other HRT products.

Tumours

• Breast cancer
Clinical and observational studies have reported an increased risk of having breast cancer diagnosed in women taking HRT for several years.

Estimates for the overall relative risks of breast cancer diagnosis given in more than 50 epidemiological studies ranged in the majority of the studies between 1 and 2.

Two large, randomised trials with CEE alone or continuously combined with MPA, showed risk estimates of 0.77 (95% confidence interval (CI): 0.59-1.01) or 1.24 (95% CI: 1.01-1.54) after 6 years of HRT use. It is unknown whether the increased risk also extends to other HRT products.

Similar increases in breast cancer diagnosis are observed, e.g. with delay of natural menopause, alcohol intake, or adiposity.

Results from a large meta-analysis showed that after stopping treatment, the excess risk will decrease with time and the time needed to return to baseline depends on the duration of prior HRT use. When HRT was taken for more than 5 years, the risk may persist for 10 years or more.

HRT increases the density of mammographic images which may adversely affect the radiological detection of breast cancer in some cases.

• Ovarian Cancer

A meta-analysis from 52 epidemiological studies reported that the overall risk of being diagnosed with ovarian cancer is slightly increased for users of HRT compared to women who have never used HRT (prospective studies: RR 1.20, 95% CI 1.15-1.26; all studies combined: RR 1.14, 95% CI 1.10-1.19). In women currently using HRT the risk of ovarian cancer was further increased (RR 1.43, 95% CI 1.31-1.56).

These associations have not been shown in all studies including randomised controlled trials, e.g. the Women's Health Initiative (WHI).

Furthermore, an effect of duration of exposure has not been consistently shown, but the risk may be more relevant with long-term use (several years).

• Endometrial cancer
Prolonged exposure to unopposed estrogens increases the risk of development of endometrial hyperplasia or carcinoma. Studies have suggested that the addition of progestogens to the regimen reduces the risk of endometrial hyperplasia and cancer (see section 5, “Pharmacodynamic properties”).

• Liver tumour
In rare cases benign, and even more rarely, malignant liver tumours have been observed after the use of hormonal substances such as those contained in HRT products. In isolated cases, these tumours led to life-threatening intra-abdominal hemorrhage. A hepatic tumour should be considered in the differential diagnosis if upper abdominal pain, enlarged liver, or signs of intra-abdominal hemorrhage occur.

Other conditions

A general association between HRT use and development of clinical hypertension has not been established. Small increases in blood pressure have been reported in women taking HRT. Clinically relevant increases are rare. However, if in individual cases a sustained clinically significant hypertension develops during the use of HRT then withdrawing the HRT may be considered.

Non-severe disturbances of liver function, including hyperbilirubinemias such as Dubin-Johnson syndrome or Rotor syndrome, need close supervision and liver function should be checked periodically. In case of deterioration of markers of liver function use of HRT should be stopped.

Women with moderately elevated levels of triglycerides need special surveillance. HRT in these women may be associated with a further increase of triglyceride levels bearing the risk of acute pancreatitis.

Although HRT may have an effect on peripheral insulin resistance and glucose tolerance, there is generally no need to alter the therapeutic regimen in diabetics using HRT. However, diabetic women should be carefully monitored while taking HRT.

Certain patients may develop undesirable manifestations of estrogenic stimulation under HRT such as abnormal uterine bleeding. Frequent or persistent abnormal uterine bleeding during treatment is an indication for endometrial assessment.

If the treatment of irregular menstrual cycles is not successful, organic diseases must be ruled out by means of adequate diagnostic measures.

Uterine fibroids (myomas) may increase in size under the influence of estrogens. If this is observed, treatment should be discontinued.

Should endometriosis be reactivated under treatment, discontinuation of therapy is recommended.

Prolactinoma should be ruled out before treatment. Close medical supervision (including periodic measurement of prolactin levels) is necessary during HRT treatment if the patient has a high risk of developing prolactinoma.

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 while taking HRT.

The following conditions have been reported to occur or deteriorate with HRT use. Although the evidence of an association with HRT use is inconclusive, women with these conditions and treated with HRT should be carefully monitored.

- Epilepsy
- Benign breast disease
- Asthma
- Migraine
- Porphyria

- Otosclerosis
- Systemic lupus erythematosus
- Chorea minor

In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema.

4.4.1 Medical examination/consultation

A complete medical history should be taken and a physical examination should be conducted prior to the initiation or reinstitution of HRT, guided by the contraindications and warnings and should be repeated periodically. The frequency and nature of these examinations should be based on established practice guidelines and be adapted to the individual woman, but should generally include pelvic organs, including routine cervical cytology, abdomen, breasts and blood pressure.

4.5 Interaction with other medicaments and other forms of interaction

Effects of other medicinal products on Progyluton

Interactions can occur with drugs that induce microsomal enzymes which can result in increased clearance of sex hormones and which may lead to changes in the uterine bleeding profile and/or reduction of the therapeutic effect.

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

phenytoin, barbiturates, primidone, carbamazepine, rifampicin and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St. John's wort.

Enzyme induction can already 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.

Substances with variable effects on the clearance of sex hormones

When co-administered with sex hormones, many HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of the estrogen or progestin. These changes may be clinically relevant in some cases.

Substances decreasing the clearance of sex hormones (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 the estrogen or the progestin or both.

Substances which undergo substantial conjugation (e.g. paracetamol), may increase the bioavailability of estradiol by competitive inhibition of the conjugation system during absorption.

***I**nteraction with alcohol*
Acute alcohol ingestion during use of HRT may lead to elevations in circulating estradiol levels.

Other forms of interaction

Laboratory tests

The use of sex steroids may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of (carrier) proteins e.g.corticosteroid-binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism, and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

4.6 Pregnancy and lactation

HRT is not indicated for use during pregnancy or lactation.

4.6.1 Pregnancy
If pregnancy occurs during medication with Progyluton, treatment should be discontinued immediately.

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

4.6.2 Lactation
Small amounts of sex hormones may be excreted in human milk.

4.7 Effects on ability to drive or use machines

No studies on the effects on the ability to drive and use machines have been performed. No effects on ability to drive and use machines have been observed in users of Cyclo-Progynova.

4.8 Undesirable effects

In addition to the adverse effects listed in the sections “Contraindications” and “Special warnings and special precautions for use”, the following undesirable effects have been reported in users of different oral HRT preparations by MedDRA System Organ Classes (MedDRA SOCs, version 8.1).

- Immune system disorders

Hypersensitivity reaction

- Metabolism and nutrition disorders

Weight increase, weight decrease

- Psychiatric disorders

Depressed mood, anxiety, libido decreased, libido increased

- Eye disorders

Visual disturbances, contact lens intolerance

- Cardiac disorders

Palpitations

- Musculoskeletal and connective tissue disorders

Muscle cramps

- Reproductive system and breast disorders

Uterine/vaginal bleeding including spotting, dysmenorrhoea, vaginal discharge, premenstrual-like syndrome, breast pain, breast tenderness, breast enlargement

- Gastrointestinal disorders

Dyspepsia, bloating, nausea, vomiting, abdominal pain, increased appetite

- Skin and subcutaneous tissue disorders

Rashes, various skin disorders (including pruritus, eczema, urticaria, acne, hirsutism, hair loss, erythema nodosum)

- Nervous system disorders

Headache, migraine, dizziness

- General disorders and administration site conditions

Edema, fatigue

In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema (see section "Special warnings and precautions for use").

Estrogen-only and combined estrogen-progestin HRT has been associated with a slightly increased risk of ovarian cancer in epidemiological studies. The risk may be more relevant with long-term use (several years) (see section 'Special warnings and precautions for use').

4.9 Overdose

Acute toxicity studies did not indicate a risk of acute adverse effects in case of inadvertent intake of a multiple of the daily therapeutic dose. Overdosage may cause nausea and vomiting and withdrawal bleeding may occur in some women. There is no specific antidote and treatment should be symptomatic.

5. PHARMACEUTICAL PROPERTIES

5.1 Pharmacodynamic properties

5.1.1 Mechanism of action

The estrogen in Progyluton is estradiol valerate, a prodrug of the natural human 17ß- estradiol. The constituent norgestrel is a synthetic progestogen. With the composition and the sequential regimen of Progyluton, including an estrogen monophase for 11 days, an estrogen-progestogen combination for 10 days and a treatment-free interval of 7 days, a menstrual cycle is established in women with an intact uterus, provided the preparation is taken regularly.

Ovulation is not inhibited during the use of Progyluton, and the endogenous production of hormones is hardly affected. The preparation can be employed in younger women to develop and regulate the cycle as well as in perimenopausal women to treat irregular uterine bleeding.

5.1.2 Pharmacodynamic effects

During the climacteric, the reduction and finally loss of ovarian estradiol secretion can result in instability of thermoregulation, causing hot flushes associated with sleep disturbance and excessive sweating, and urogenital atrophy with symptoms of vaginal dryness, dyspareunia and urinary incontinence. Less specific but often mentioned as part of the climacteric syndrome are symptoms like anginal complaints, palpitations, irritability, nervousness, lack of energy and concentration abilities, forgetfulness, loss of libido and joint and muscle pain.

5.1.3 Clinical efficacy and safety

Hormone replacement therapy (HRT) alleviates many of these symptoms of estradiol deficiency in the menopausal woman.

HRT with an adequate estrogen dosage like in Progyluton reduces bone resorption and retards or halts postmenopausal bone loss. Long–term treatment with HRT has been shown to reduce the risk of peripheral fractures in postmenopausal women. When HRT is discontinued, bone mass declines at a rate comparable to that in the immediate postmenopausal period. There is no evidence that HRT restores bone mass to premenopausal levels. HRT also has a positive effect on skin collagen content and skin thickness and can retard the process of skin wrinkling.

The addition of a progestogen to an estrogen replacement regimen for at least 10 days per cycle as in Progyluton reduces the risk of endometrial hyperplasia and the attendant risk of adenocarcinoma in women with an intact uterus. The addition of a progestogen to an estrogen replacement regimen has not been shown to interfere with the efficacy of estrogen for its approved indications.

Observational studies and the Women's Health Inititative (WHI) trial on conjugated equine estrogens (CEE) plus medroxyprogesterone acetate (MPA) suggest a reduction of colon cancer morbidity in postmenopausal women taking HRT. In the WHI trial on CEE mono-therapy, a risk reduction was not observed. It is unknown whether these findings also extend to other HRT products.

5.2 Pharmacokinetic properties

5.2.1 Estradiol valerate
5.2.1.1 Absorption
Estradiol valerate is rapidly and completely absorbed. The steroid ester is cleaved into estradiol and valeric acid during absorption and the first liver passage. At the same time, estradiol undergoes extensive further metabolism, e.g. into estrone, estriol and estrone sulfate. Only about 3 % of estradiol becomes bioavailable after oral administration of estradiol valerate. Food does not affect the bioavailability of estradiol.

5.2.1.2 Distribution
Maximum concentrations of estradiol in serum of approx. 30 pg/ml are generally reached between 4-9 hours after tablet intake. Within 24 hours after tablet intake, serum levels of estradiol declined to concentrations of about 15 pg/ml. Estradiol binds to albumin and the sex hormone binding globulin (SHBG). However, the binding to SHBG is lower than that of levonorgestrel. The unbound fraction of estradiol in serum is about 1-1.5 % and the SHBG-bound fraction is in the range of 30-40 %.

The apparent volume of distribution of estradiol after single intravenous administration is about 1 l/kg.

5.2.1.3 Metabolism
After the ester cleavage of the exogenously administered estradiol valerate, the metabolism of the drug follows the biotransformation pathways of endogenous estradiol. Estradiol is mainly metabolized in the liver but also extra-hepatically e.g. in gut, kidney, skeletal muscles and target organs. These processes involve the formation of estrone, estriol, catecholestrogens and sulfate and glucuronide conjugates of these compounds, which are all distinctly less estrogenic or even non-estrogenic.

5.2.1.4 Elimination
The total serum clearance of estradiol following single intravenous administration, shows high variability in the range of 10-30 ml/min/kg. A certain proportion of estradiol metabolites are excreted in the bile and undergo a so-called enterohepatic circulation. Ultimately estradiol metabolites are mainly excreted as sulfates and glucuronides with the urine.

5.2.1.5 Steady state conditions
In relation to the single dose, approximately two times higher serum levels of estradiol are observed after multiple administration. On average, the concentration of estradiol varies between 30 (minimum levels) and 60 pg/ml (maximum levels). Estrone, as a less estrogenic metabolite, reaches about 8-times higher concentrations in serum, estrone sulfate reaches approximately 150-times higher concentrations.

After stopping the treatment with Progyluton, pre-treatment levels of estradiol and estrone are reached within 2-3 days. No distinct difference in the estrogen levels is observed between the treatment phase with estradiol valerate alone or in combination with norgestrel.

5.2.2 Norgestrel
5.2.2.1 Absorption
After oral administration, norgestrel is absorbed rapidly and completely. The active component of the racemate norgestrel is levonorgestrel which becomes completely bioavailable from the racemate and accounts for about half of the dose of norgestrel.

5.2.2.2 Distribution
On an average, maximum concentrations of levonorgestrel in serum of 7-8 ng/ml are already reached within 1-1.5 hours after a single administration of Progyluton. Subsequently, serum levels of levonorgestrel decline biphasically with a mean terminal half-life of 27 hours and reach minimum concentrations of about 1 ng/ml 24 hours post dose.

Levonorgestrel binds to albumin and SHBG. Only about 1-1.5 % of the total levonorgestrel concentration in serum is not protein-bound. The relative fractions of free, albumin- and SHBG-bound levonorgestrel are strongly dependent on the concentration of SHBG in serum. After induction of the binding proteins, the fraction bound to SHBG increases whereas the unbound fraction and that bound to albumin decreases. At the end of the estrogen monophase of the Progyluton treatment cycle, the concentration of SHBG reaches the highest levels in serum which then decreases to the lowest levels at the end of the combination phase.

Accordingly, the free fraction of levonorgestrel amounts to about 1 % at the beginning and about 1.5 % at the end of the combination phase. The corresponding fractions of levonorgestrel bound to SHBG are 70 and 65 %, respectively.

5.2.2.3 Metabolism
Norgestrel is extensively metabolized. The most important metabolic pathways of the active substance levonorgestrel (LNG) 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. Pharmacologically active metabolites are not known.

5.2.2.4 Elimination
The total clearance rate of levonorgestrel from serum is 1 ml/min/kg. With a half-life of about 1 day, approximately the same proportions of the metabolites of norgestrel are excreted with the urine and the bile.

5.2.2.5 Steady-state conditions
Based on the elimination half-life of levonorgestrel in serum of about 24 hours, an accumulation of the active substance in serum would be expected. Accordingly, elevated trough levels of about 1 ng/ml are observable after repeated administration. However, due to the simultaneous change in the protein binding capacity during treatment (decrease in SHBG concentration), the area under the serum levels-time course of levonorgestrel does not really differ between the beginning and the end of the 10-day treatment phase with the estrogen/progestogen combination. Thus, no accumulation of levonorgestrel in serum is observed after multiple administration of Progyluton.

6. PHARMACEUTICAL PARTICULARS

6.1 Shelf Life
Please refer to labels.

6.2 Storage Conditions
Store all drugs properly and keep them out of reach of children.

6.3 Manufacturer
Bayer Weimar GmbH und Co. KG
Dobereiner Strabe 20, D-99427
Weimar, Germany

Date of Revision
14 December 2021

If you would like to report a side effect for any Bayer Pharmaceutical or Consumer Health product, you can do it easily using our online reporting portal: https://safetrack-public.bayer.com/ or scan the QR code available below. Please also remember to seek medical advice directly from your doctor or pharmacist.

SafeTrack