1. NAME OF THE MEDICINAL PRODUCT

PROGYLUTON
Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Calendar-pack containing 11 white tablets of 2 mg estradiol valerate each, plus 10 light brown tablets of 2 mg estradiol valerate and 0.5 mg norgestrel each.

3. PHARMACEUTICAL FORM
Coated tablets.

4. CLINICAL PARTICULARS
4.1 Therapeutic indication
Two phase preparation for climacteric and cycle disturbances.

4.2 Posology and method of administration
Progyluton is a cyclic HRT product. One tablet is to be taken orally once a day for 21 days, followed by a 7 day tablet free interval. Therefore each new pack is started after a 28 day cycle. The white tablets should be taken from days 1 to 11 followed by the brown tablets from days 12 to 21. It is recommended that the tablets are taken at the same time every day.

For initiation and continuation of treatment of peri- and post-menopausal symptoms the lowest effective dose for the shortest duration (see also Section 4.4) should be used.

For women still having periods, the first tablet should be taken on the 5th day of their menstrual period. If menstruation has stopped, or is infrequent or sporadic, then the first tablet can be taken any time.

If the patient is being transferred from a continuous HRT product, the patient may start Progyluton on any convenient day. For those transferring from a cyclic or sequential product, Progyluton should be started following completion of the previous regimen.

If a tablet is missed, it should be taken as soon as possible, unless it is more than 12 hours late. In this case the missed tablet should be left in the pack and the next tablet taken at the right time. Missing a dose may result in breakthrough bleeding or spotting.

Unless there is a previous diagnosis of endometriosis, it is not recommended that progestagen-containing HRT be given to hysterectomised women.

Children and adolescents
Progyluton is not indicated for use in children and adolescents.

Geriatric patients
There are no data suggesting a need for dosage adjustment in women aged 65 years or older (see section 4.4 Special warnings and precautions for use.

Patients with hepatic impairment
Progyluton has not been specifically studied in patients with hepatic impairment. (see 4.3 (Contraindications

Patients with renal impairment
Progyluton has not been specifically studied in renally impaired patients. Available data do not suggest a need for dosage adjustment in this patient population.

4.3 Contraindications
Pregnancy and lactation
Undiagnosed vaginal bleeding
Known, past or suspected cancer of the breast
Known or suspected oestrogen-dependent malignant tumours (e.g. endometrial cancer)
Untreated endometrial hyperplasia
Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction)-
Previous or current venous thromboembolism (deep venous thrombosis, pulmonary
embolism)
Known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency, see
section 4.4)
Known hypersensitivity to any of the components of Progyluton
Acute liver disease or a history of liver disease unless liver function tests have returned to
normal
Porphyria

4.4 Special warnings and special precautions for use
For the treatment of postmenopausal symptoms, HRT should only be initiated for
symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks
and benefits should be undertaken at least annually and HRT should only be continued as
long as the benefit outweighs the risk.

Evidence regarding the risks associated with HRT in the treatment of premature
menopause is limited.

Due to the low level of absolute risk in younger women, however, the balance of benefits
and risks for these women may be more favourable than in older women.

Medical Examination/Follow-up
Before initiating or reinstating HRT, a complete personal and family medical history
should be taken. Physical examination (including pelvic and breast) should be guided by
this and by the contraindications (section 4.3) and warnings for use (section 4.4). During
treatment periodic check-ups are recommended of a frequency and nature adapted to the
individual woman. Women should be advised what changes in their breasts should be
reported to their doctor or nurse (see ‘breast cancer’ below). Investigations, including
appropriate imaging tools, e.g. mammography, should be carried out in accordance with
currently accepted screening practices, modified to the clinical needs of the individual.

Before starting treatment, pregnancy should be excluded. If withdrawal bleeding fails to
occur at about 28-day intervals, the possibility of pregnancy should be considered in peri-
menopausal women.

The patient may experience blood loss after completing each pack.

Conditions that need supervision
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 monitored. It should be taken into account that these conditions may recur or may be aggravated during treatment with Progyluton, in particular:

leiomyoma (uterine fibroids) or endometriosis
risk factors for thromboembolic disorders (see below)
risk factors for oestrogen dependent tumours, e.g. 1st degree heredity for breast cancer
hypertension
liver disorders (e.g. liver adenoma)
diabetes mellitus with or without vascular involvement
cholelithiasis
migraine or severe headache
systemic lupus erythematosus
chorea minor
a history of endometrial hyperplasia (see below)
epilepsy
asthma
otosclerosis
hereditary angioedema

Close medical supervision (including periodic measurement of prolactin levels) is necessary if the patient suffers from prolactinoma.

**Reasons for immediate withdrawal of therapy**

Therapy should be discontinued in case a contra-indication is discovered and in the following situations:
significant increase in blood pressure
pregnancy
jaundice or deterioration in liver function.
migrainous headaches occur for the first time

**Endometrial Hyperplasia**

In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among oestrogen-only users varies from 2-to 12-fold greater compared with non-users, depending on the duration of treatment and oestrogen dose (see section 4.8). After stopping treatment risk may remain elevated for at least 10 years.

The addition of a progestagen for 10 days per cycle in non-hysterectomised women reduces, but does not eliminate, this risk.

Breakthrough bleeding and spotting may occur during the first few months of treatment, but if this occurs after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated. This may include an endometrial biopsy to exclude endometrial malignancy.

**Breast Cancer**

The overall evidence suggests an increased risk of breast cancer in women taking combined oestrogenprogestagen and possibly also oestrogen-only HRT, that is dependent on the duration of taking HRT.
Combined oestrogen-progestagen therapy
The randomised placebo-controlled trial the (Women’s Health Initiative study), and epidemiological studies are consistent in finding an increased risk of breast cancer in women taking combined oestrogen-progestagen for HRT that becomes apparent after about 3 years (see section 4.8).

Oestrogen-only therapy
The WHI trial found no increase in the risk of breast cancer in hysterectomised women using oestrogen-only HRT. Observational studies have mostly reported a small increase in risk of having breast cancer diagnosed that is substantially lower than that found in users of oestrogen-progestagen combinations (see section 4.8).

The excess risk becomes apparent within a few years of use but returns to baseline within a few (at most five) years after stopping treatment.

HRT, especially oestrogen-progestagen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

Ovarian cancer
Ovarian cancer is much rarer than breast cancer. Long-term (at least 5-10 years) use of oestrogen–only HRT products has been associated with a slightly increased risk of ovarian cancer (see section 4.8). Some studies including the WHI trial suggest that the long-term use of combined HRTs may confer a similar, or slightly smaller, risk (see section 4.8).

Venous Thromboembolism (VTE)
HRT is associated with a 1.3-3 fold risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of HRT than later (section 4.8).

Patients with known thrombophilic states have an increased risk of VTE and HRT may add to this risk. HRT is therefore contraindicated in these patients (see section 4.3).

Generally recognised risk factors for VTE include use of oestrogens, older age, major surgery, prolonged immobilisation, obesity (BMI >30kg/m2) pregnancy/postpartum period, systemic lupus erythematosus (SLE), and cancer. There is no consensus about the possible role of varicose veins in VTE.

As in all postoperative patients, prophylactic measures need to be considered to prevent VTE following surgery. If prolonged immobilisation is to follow elective surgery temporarily stopping HRT 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilised.

In women with no personal history of VTE but with a first degree relative with a history of thrombosis at a young age, screening may be offered after careful counselling regarding its limitations (only a proportion of thrombophilic defects are identified by screening).

If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is “severe” (e.g. antithrombin, protein S, or protein C deficiencies or a combination of defects) HRT is contraindicated.

Women already on chronic anticoagulant treatment require careful consideration of the benefit-risk of use of HRT
If VTE develops after initiating therapy the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g. painful swelling of leg, sudden pain in chest, dyspnoea)

**Coronary Arterial Disease (CAD)**
There is no evidence from randomised controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined oestrogen-progestagen or oestrogen only HRT.

Combined oestrogen-progestagen therapy
The relative risk of CAD during use of combined oestrogen+progestagen HRT is slightly increased. As the baseline absolute risk of CAD is strongly dependent on age, the number of extra cases of CAD due to oestrogen+progestagen use is very low in healthy women close to menopause, but will rise with more advanced age.

Oestrogen-only
Randomised controlled data found no increased risk of CAD in hysterectomised women using oestrogen-only therapy.

**Ischaemic Stroke**
Combined oestrogen-progestagen and oestrogen-only therapy are associated with an up to 1.5-fold increase in risk of ischaemic stroke. The relative risk does not change with age or time since menopause. However, as the baseline risk of stroke is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age (see section 4.8).

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

**Other Conditions**
Oestrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed. Patients with terminal renal insufficiency should be closely observed since it is expected that the level of circulating active ingredients of Progyluton may increase.

Women with pre-existing hypertriglyceridemia should be followed closely during oestrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oestrogen therapy in this condition.

Oestrogens increase thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone as measured by protein-bound iodine (PBI), T4 levels (by column or by radio-immunoassay), or T3 levels (by radio-immunoassay). T3 resin uptake is decreased reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Other binding proteins may be elevated in serum, i.e. corticoid binding globulin (CBG), sex-hormone-binding globulin (SHBG) leading to increased circulating corticosteroids and sex steroids, respectively. Free or biological active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-I-antitrypsin, ceruloplasmin).
HRT use does not improve cognitive function. There is some evidence of increased risk of probable dementia in women who start using continuous combined or oestrogen-only HRT after the age of 65.

Progyluton cannot be used as a contraceptive.

Hormonal contraception should be stopped when treatment with Progyluton is started and the patient should be advised to take non-hormonal contraceptive precautions.

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

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

4.5 Interaction with other medicinal and other forms of interaction
The metabolism of oestrogens and progestagens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepine), and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz).

Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones. Herbal preparations containing St John's Wort (Hypericum Perforatum) may induce the metabolism of oestrogens and progestagens.

Clinically, an increased metabolism of oestrogens and progestagens may lead to decreased efficacy and changes in uterine bleeding profile.

The requirement for oral antidiabetics or insulin can change.

4.6 Pregnancy and lactation
Progyluton is not indicated for use during pregnancy or lactation. If pregnancy occurs during medication with Progyluton, treatment should be discontinued immediately. No data on exposed pregnancies are available. Studies in animals have not shown reproductive toxicity.

The results of most epidemiological studies to-date, relevant to inadvertent foetal exposure to combinations of oestrogens and progestagens indicate no teratogenic or foetotoxic effect.

4.7 Effects on ability to drive and use machines
No observed effects.

4.8 Undesirable effects
During the first few months treatment, breakthrough bleeding, spotting and breast tenderness or enlargement can occur. These are usually temporary and normally disappear after continued treatment.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥1/100, &lt;1/10</td>
<td>≥1/1,000, &lt;1/100</td>
<td>≥1/10,000, &lt;1/1,000</td>
</tr>
<tr>
<td>MedDRA v. 8.0</td>
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<td>-----------------------------------------------</td>
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<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity reaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Weight increase or weight decrease</td>
<td>Anxiety, libido decreased or libido increased</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Depressed mood</td>
<td>Anxiety, libido decreased or libido increased</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Dizziness</td>
<td></td>
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<tr>
<td>Eye disorders</td>
<td>Visual disturbances</td>
<td>Migraine</td>
<td></td>
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<tr>
<td>Cardiac disorders</td>
<td>Palpitations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Abdominal pain, nausea</td>
<td>Dyspepsia</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash, pruritus</td>
<td>Erythema nodosum, urticaria</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and subcutaneous tissue disorders</td>
<td></td>
<td>Hirsutism, acne</td>
<td></td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Uterine/vaginal bleeding including spotting (bleeding irregularities usually subside during continued treatment)</td>
<td>Breast pain, breast tenderness</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Edema</td>
<td>Fatigue</td>
<td></td>
</tr>
</tbody>
</table>

The most appropriate MedDRA term (version 8.0) to describe a certain reaction is listed. Synonyms or related conditions are not listed, but should be taken into account as well.

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

Other reactions have also been reported in association with oestrogen/progestagen treatment:
- Oestrogen-dependent neoplasms benign and malignant, e.g. breast* (see below) and endometrial** (see below) cancer
- Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism, is more frequent among hormone replacement therapy users than among non-users. For further information, see section 4.3 Contraindications and 4.4 Special warnings and precautions for use
- Myocardial infarction and stroke
- Gall bladder disease
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura
- Probable dementia (see Section 4.4)
In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema.

Breast Cancer

According to evidence from a large number of epidemiological studies and one randomised placebo-controlled trial, the Women’s Health Initiative (WHI), the overall risk of breast cancer increases with increasing duration of HRT use in current or recent HRT users.

For oestrogen-only HRT, estimates of relative risk (RR) from a reanalysis of original data from 51 epidemiological studies (in which >80% of HRT use was oestrogen-only HRT) and from the epidemiological Million Women Study (MWS) are similar at 1.35 (95%CI 1.21-1.49) and 1.30 (95%CI 1.21-1.40), respectively.

For oestrogen plus progestagen combined HRT, several epidemiological studies have reported an overall higher risk for breast cancer than with oestrogens alone.

The MWS reported that, compared to never users, the use of various types of oestrogen-progestagen combined HRT was associated with a higher risk of breast cancer (RR = 2.00, 95%CI: 1.88 – 2.12) than use of oestrogens alone (RR = 1.30, 95%CI: 1.21 – 1.40) or use of tibolone (RR=1.45; 95%CI 1.25-1.68).

The WHI trial reported a risk estimate of 1.24 (95%CI 1.01 – 1.54) after 5.6 years of use of oestrogen-progestagen combined HRT (CEE + MPA) in all users compared with placebo.

The absolute risks calculated from the MWS and the WHI trial are presented below:

The MWS has estimated, from the known average incidence of breast cancer in developed countries, that:

- For women not using HRT, about 32 in every 1000 are expected to have breast cancer diagnosed between the ages of 50 and 64 years.
- For 1000 current or recent users of HRT, the number of additional cases during the corresponding period will be
  - For users of oestrogen-only replacement therapy between 0 and 3 (best estimate = 1.5) for 5 years’ use
  - Between 3 and 7 (best estimate = 5) for 10 years’ use.
- For users of oestrogen plus progestagen combined HRT, between 5 and 7 (best estimate = 6) for 5 years’ use
  - Between 18 and 20 (best estimate = 19) for 10 years’ use.

The WHI trial estimated that after 5.6 years of follow-up of women between the ages of 50 and 79 years, an additional 8 cases of invasive breast cancer would be due to oestrogen-progestagen combined HRT (CEE + MPA) per 10,000 women years.

According to calculations from the trial data, it is estimated that:

- For 1000 women in the placebo group, about 16 cases of invasive breast cancer would be diagnosed in 5 years.
- For 1000 women who used oestrogen + progestagen combined HRT (CEE + MPA), the number of additional cases would be between 0 and 9 (best estimate = 4) for 5 years’ use.
The number of additional cases of breast cancer in women who use HRT is broadly similar for women who start HRT irrespective of age at start of use (between the ages of 45-65) (see section 4.4).

Endometrial Cancer
** In women with an intact uterus, the risk of endometrial hyperplasia and endometrial cancer increases with increasing duration of use of unopposed oestrogens. According to data from epidemiological studies, the best estimate of the risk is that for women not using HRT, about 5 in every 1000 are expected to have endometrial cancer diagnosed between the ages of 50 and 65. Depending on the duration of treatment and oestrogen dose, the reported increase in endometrial cancer risk among unopposed oestrogen users varies from 2-to 12-fold greater compared with non-users. Adding a progestagen to oestrogen-only therapy greatly reduces this increased risk.

4.9 Overdose
There have been no reports of ill-effects from overdosage. There are no specific antidotes, and therefore treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
The estrogen in Progyluton is estradiol valerate, a prodrug of the natural human 17ß- estradiol. Synthetic 17 β-estradiol, is chemically and biologically identical to endogenous human estradiol. It substitutes for the loss of oestrogen production in menopausal women, and alleviates menopausal symptoms.

Oestrogens prevent bone loss following menopause or Ovariectomy.

The constituent norgestrel is a synthetic progestogen.

As oestrogens promote the growth of the endometrium, unopposed oestrogen increase the risk of endometrial hyperplasia and cancer. The addition of a progestagen greatly reduces the oestrogen induced risk of endometrial hyperplasia in non-hysterectomised women.

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.

Hormone replacement therapy (HRT) alleviates many of the symptoms of estradiol deficiency in menopausal woman such as hot flushes, excessive sweating, urogenital atrophy with symptoms of vaginal dryness and dyspareunia.

Relief of menopausal symptoms was achieved by the third cycle after initiation of treatment. In a clinical trial 314 subjects were enrolled and treated with 2 mg EV/0.5 mg NG, 235 subjects completed the study. 93.3% of the subjects who completed showed a reduction of the mean number of hot flushes per week of at least 50% after 3 cycles of treatment. 61.1% of subjects had no hot flushes any more at cycle 3. In another clinical trial one third of the subjects was free of vasomotor symptoms after one treatment cycle.

The Kupperman Index, related to the most common menopausal complaints which are weighted according to their importance, significantly decreased from baseline at cycle 3.
Data from clinical trials indicate that regular monthly withdrawal bleeding occurred in approximately 90% of women. The mean duration of withdrawal bleeding was 3.8 days. Withdrawal bleeding starts on average 3.1 days after the last pill of the progestagen phase. The amenorrhea rate (no bleeding or spotting) is less than 5%.

Oestrogen deficiency at menopause is associated with an increasing bone turnover and decline in bone mass.

The effect of oestrogens on the bone mineral density is dose-dependent. Protection appears to be effective for as long as treatment is continued. After discontinuation of HRT, bone mass is lost at a rate similar to that in untreated women.

Evidence from the WHI trial and meta-analysed trials shows that current use of HRT, alone or in combination with a progestagen – given to predominantly healthy women – reduces the risk of hip, vertebral, and other osteoporotic fractures. HRT may also prevent fractures in women with low bone density and/or established osteoporosis, but the evidence for that is limited.

5.2 Pharmacokinetic properties

**Estradiol valerate**

**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.

**Distribution**

Following single administration of 2mg estradiol valerate, maximum concentrations of estradiol in serum of approx. 25-30 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.

**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 extrahepatically e.g. in gut, kidney, skeletalmuscles 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 nonestrogenic.

**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.
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.

Norgestrel
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.

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.

Biotransformation
Norgestrel is completely metabolized. Biotransformation of the active substance levonorgestrel follows the known pathways of steroid metabolism. Pharmacologically active metabolites are not known.

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.

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.

5.3 Preclinical safety data
None

6 PHARMACEUTICAL PARTICULARS
6.1 list of excipients
Lactose monohydrate, maize starch, polyvidone 25000, talc, magnesium stearate, sucrose, polyvidone 700000, macrogol 6000, calcium carbonate, glycerol 85%, titanium dioxide (E171), ferric oxide yellow (E172), ferric oxide red (E172), montanlycol wax

6.2 Incompatibilities
None known

6.3 Shelf life
5 years

6.4 Special precautions for storage
Do not store above 25°C.

6.5 Nature and contents of container
Each pack consists of aluminium foil and PVC and contains 21 tablets.

6.6 Instructions for use and handling (and disposal)
No special requirements for disposal.

MANUFACTURER:
Bayer Weimar GmBH und Co. KG, Weimar, Germany

REGISTRATION HOLDER:
Bayer Israel Ltd., 36 Hacharash St., Hod Hasharon 45240