SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Progynova® 2 mg coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Progynova 2 mg tablet contains 2 mg estradiol valerate.

Excipient with known effect: lactose monohydrate 46.22 mg and sucrose 33.98 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet, coated

Product descriptions:

Progynova 2 mg tablet: White, round, biconvex, sugar-coated tablet (about 7 mm in diameter).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hormone replacement therapy (HRT) when the symptoms of estrogen deficiency are due to natural or surgically induced menopause.

Prevention of osteoporosis in postmenopausal women.

4.2 Posology and method of administration

Start of treatment

In hysterectomized patients therapy may be started on any suitable day.

If the patient has an intact uterus and is still menstruating, a combination regimen with Progynova and a progestin should begin within the first 5 days of menstruation (see Combination regimen).
Patients with amenorrhea or very infrequent periods or postmenopausal patients may start therapy at any time, provided that pregnancy has been excluded.

For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration (see also section 4.4) should be used.

When changing hormone replacement therapy from another preparation to Progynova, the previous treatment period must be completed before transferring to Progynova.

Posology

*Cyclic therapy:*1 tablet once daily for 21 days, followed by a 7-day break.

*Continuous therapy:*1 tablet once daily continuously without a break.

Combination regimen with Progynova and progestin: Estrogen alone should not be given to women with an intact uterus. For such patients, estrogen is recommended to be combined with a progestin for 10–14 days every 4 weeks (sequential combined therapy) or every day (continuous combined therapy).

Pediatric population
Progynova is not indicated for use in children and adolescents.

Elderly patients
Available data does not suggest a need for dosage adjustment in elderly patients. For women over 65 years, see section 4.4.

Hepatic insufficiency
The use of the product has not been specifically studied in patients with hepatic insufficiency. Progynova is contraindicated in women with a severe hepatic disease (see section 4.3).

Renal insufficiency
The use of the product has not been specifically studied in patients with renal insufficiency. Available data does not suggest a need for dosage adjustment in this patient population.

Missed tablets
If the patient forgets to take a tablet at the usual time, she should take it within 12–24 hours. If therapy is discontinued for a longer period, irregular bleeding may occur.

Method of administration

Oral use.
The tablets should be swallowed whole with liquid.
The tablets can be taken at any time of the day as long as they are taken every day at approximately the same time.

4.3 Contraindications

Hormone replacement therapy (HRT) should not be started and the use of the product should be immediately discontinued if the patient presents with any of the conditions listed below.

- Known, past or suspected breast cancer
- Known or suspected estrogen-dependent malignant tumor (e.g. endometrial cancer)
- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
- Previous or acute thromboembolism (deep venous thrombosis, pulmonary embolism)
- Known thrombophilic disorder/condition (e.g. protein C, protein S or antithrombin deficiency, see section 4.4)
- Active or recent arterial thromboembolic disease (e.g. angina pectoris or myocardial infarction)
- Acute or previous liver disease as long as liver function tests have failed to return to normal
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

- Porphyria

4.4 Special warnings and precautions for use

For the treatment of postmenopausal symptoms, HRT should be initiated only if the symptoms adversely affect the quality of life. In all cases, the risks and benefits of the treatment should be evaluated once a year and HRT should only be continued as long as the benefits outweigh the risks.

Results regarding the risks associated with HRT in the treatment of premature menopause are limited. Due to the low level of absolute risk in younger women, the balance of benefits and risks for these women may be more favorable than for older women.

Medical examination / follow-up

Before initiating or reinstituting HRT, a personal and family medical history should be taken. The physical examination (including a pelvic and breast examination) should be guided by the medical history and by the contraindications and warnings for use. During treatment, regular check-ups are recommended of a frequency and nature adapted to the individual woman. The patients should be advised on what kind of changes in their breasts should be reported to the doctor or nurse (see 'Breast cancer' below). Breast investigations, including mammography, should be carried out in accordance with currently accepted screening recommendations, modified to the medical needs of the individual.

Conditions which need supervision

If any of the following conditions are present or have occurred previously and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised as these conditions may recur or be aggravated during treatment with Progynova:
- Leiomyoma (uterine fibroids) or endometriosis
- Risk factors for thromboembolism (see below)
- Risk factors for estrogen-dependent tumors, such as 1st degree heredity for breast cancer
- Hypertension
- Liver disorders (such as liver adenoma)
- Diabetes mellitus with or without vascular changes
- Cholelithiasis
- Migraine or (severe) headache
- Systemic lupus erythematosus (SLE)
- History of endometrial hyperplasia (see below)
- Epilepsy
- Asthma
- Otosclerosis

Reasons for immediate withdrawal of therapy

Therapy should be discontinued in case a contraindication is discovered and in the following situations:
- Jaundice or hepatic insufficiency
- Significant increase in blood pressure
- First occurrence of migraine-type headache
- Pregnancy

Endometrial hyperplasia and carcinoma

In women with intact uterus the risk of endometrial hyperplasia and carcinoma is increased when estrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among women using an estrogen-only product varies from 2- to 12-fold greater (depending on the

duration of treatment and the estrogen dose) compared with women not using an estrogen product (see section 4.8). After stopping treatment, the risk may remain elevated for at least 10 years.

The addition of a progestin for at least 12 days per month/cycle (28 days) or as continuous combined therapy in non-hysterectomized women; protects from the increased risk associated with estrogen-only therapy.

The protective effect on the endometrium of a progestin included in an oral 2 mg dose of estrogen has not been investigated.

Breakthrough bleeding and spotting may occur during the first months of treatment. If breakthrough bleeding or spotting appears after some time on therapy or continues after treatment has been discontinued, the reason should be investigated. Endometrial biopsy may be necessary to exclude malignancy.

Therapy with estrogen alone may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore, the addition of a progestin to estrogen replacement therapy should be considered in women who have undergone hysterectomy because of endometriosis if they are known to have residual endometriosis.

Breast cancer

The overall evidence shows an increased risk of breast cancer in women receiving combined estrogen-progestin products or estrogen only. The risk is dependent on the duration of the treatment.

Combined therapy containing estrogen and progestin
A randomized placebo-controlled trial (Women's Health Initiative study (WHI)) and a meta-analysis of prospective epidemiological studies are consistent in finding an increased risk of breast cancer in women using combined therapy of estrogen and progestin (see section 4.8). The risk increases after about 3 (1–4) years of use.

Estrogen-only therapy
The WHI trial found no increase in the risk of breast cancer in hysterectomized women using estrogen-only HRT. Observational studies have reported a small increase in the number of breast cancer diagnoses that is lower than that found in users of a combination of estrogen and progestin (see section 4.8).

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

HRT, especially the combination of estrogen and progestin, increases the density of the mammary gland in mammographic images, which may adversely affect the radiological detection of breast cancer.

Ovarian cancer

Ovarian cancer is much rarer than breast cancer.

A large meta-analysis of epidemiological data suggests a slightly increased risk in women using HRT (estrogen alone or a combination of estrogen and progestin). The increased risk becomes apparent within 5 years of use and diminishes over time after stopping the treatment.

Some other studies (including the WHI trial) suggest that the use of combined HRT may be associated with a similar or slightly smaller risk (see section 4.8).

Venous thromboembolism (VTE)

HRT is associated with a 1.3- to 3-fold risk of developing VTE (such as deep vein thrombosis or pulmonary embolism). The occurrence of VTE is more likely during the first year of treatment than later (see section 4.8).

Patients with a known thrombophilic state 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 recognized risk factors for VTE include use of estrogen, older age, major surgical procedure, prolonged immobilization, overweight (BMI > 30 kg/m^2), 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 the surgery leads to prolonged immobilization, temporary discontinuation of HRT 4–6 weeks prior to surgery is recommended. Treatment should not be restarted until the patient is completely mobilized.

In women with no personal history of VTE but with a first degree relative with a history of venous thrombosis at young age, screening may be offered after careful consideration of its limitations (only a proportion of thrombophilic disorders can be identified by screening). If a thrombophilic defect is identified to be prevalent in the family or if the defect is 'severe' (e.g. antithrombin, protein S or protein C deficiencies, or a combination of these), HRT is contraindicated.

The benefits and risks of HRT should be carefully assessed in women using permanent anticoagulant therapy.

If VTE develops after initiating therapy, treatment must be discontinued. Patients should be told to contact their doctor immediately if they notice symptoms of thromboembolism (e.g. painful swelling of a leg, sudden pain in the chest, dyspnea).

Coronary artery disease (CAD)

There is no evidence from randomized controlled trials that HRT would provide protection against myocardial infarction in healthy women or in women with CAD using HRT (either a combination of estrogen and progestin or estrogen alone).

Combined therapy containing estrogen and progestin

The relative risk of CAD during the use of combined HRT is slightly increased. As the baseline absolute risk of CAD is strongly dependent on age, the number of CAD cases caused by combined therapy is very low in healthy women close to menopause but the number increases with age.

Estrogen-only therapy

Randomized controlled data found no increased risk of CAD in hysterectomized women using estrogen-only therapy.

Cerebral infarction

Combined therapy containing estrogen and progestin as well as estrogen-only therapy are associated with an up to 1.5-fold increase in the risk of cerebral infarction. 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).

Other conditions

- Estrogens may cause fluid retention, and therefore patients with cardiac or renal insufficiency should be carefully observed.
- Women with hypertriglyceridemia should be followed closely during estrogen replacement or other hormone replacement therapy since rare cases of notable increases of plasma triglycerides leading to pancreatitis have been reported during estrogen therapy.
- Estrogens increase thyroglobulin (TBG) levels, leading to increased circulating total thyroid hormone, as measured by protein bound iodine (PBI), T_4 levels (by colony assay or radioimmunoassay) or T_3 levels (by radioimmunoassay). T_3 resin uptake is decreased, reflecting the elevated thyroglobulin levels. Free T_4 and free T_3 concentrations are unaltered. Other binding proteins, e.g. corticosteroid binding globulin (CBG) and sex hormone binding globulin (SHBG), may be elevated in serum, leading to increased circulating corticosteroids and sex hormones, respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins (angiotensinogen/renin substrate, $alpha_1$-antitrypsin, ceruloplasmin) may be increased.
- HRT does not improve cognitive function. There is some evidence of increased risk of probable dementia in women who start using the combined or estrogen-only therapy after the age of 65.

The tablets contain lactose and sucrose. Patients with rare hereditary problems of fructose or galactose intolerance, total lactase deficiency, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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

Effects of other medicinal products on Progynova

Substances increasing the clearance of sex hormones (diminished efficacy by enzyme induction):

The metabolism of estrogens (and progestins) may be accelerated by concomitant use of drugs known to induce enzyme systems (specifically cytochrome P450) such as anticonvulsants (e.g. barbiturates, phenytoin, primidone, carbamazepine) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz) and possibly also felbamate, griseofulvin, oxcarbamazepine, topiramate, and herbal remedies containing St. John's wort (*Hypericum perforatum*).
The increased metabolism of estrogens and progestins may impair the therapeutic effect of the product and cause changes in the uterine bleedings.

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

Substances with variable effects on the clearance of sex hormones

Many combinations of HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors, including combinations with HCV protease inhibitors, can increase or decrease the plasma concentrations of estrogen. The overall effect of these changes may be clinically relevant in some cases.

Therefore, the prescribing information of concomitant HIV or HCV protease inhibitors should be consulted to identify potential interactions.

Substances decreasing the clearance of sex hormones (enzyme inhibitors):

Strong or 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 the plasma concentrations of the estrogen.
Preparations which undergo substantial conjugation (e.g. paracetamol) can increase the bioavailability of estradiol by competitive inhibition of the conjugation system during absorption.

In individual cases the requirement for oral antidiabetics or insulin can change as a result of the effect on glucose tolerance.

Other interactions

Laboratory tests

The use of sex hormones may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function; plasma levels of 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. For more information, see section 4.4 Other conditions.

4.6 Fertility, pregnancy and lactation

Pregnancy

Progynova must not be used during pregnancy. If pregnancy occurs during treatment, the use of the product must be stopped immediately.

Most epidemiological studies to date have not indicated that inadvertent exposure during pregnancy would have teratogenic or fetotoxic effects.

Breastfeeding

Progynova must not be used during breastfeeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The serious undesirable effects associated with the use of HRT are also described in section 4.4 Special warnings and precautions for use.

The table below lists the undesirable effects that have been reported in users of HRT by MedDRA system organ classes.

System Organ Class	**Common (≥ 1/100, < 1/10)**	**Uncommon (≥ 1/1,000, < 1/100)**	**Rare (< 1/1,000)**

Immune system disorders		Hypersensitivity reactions	
Metabolism and nutrition disorders	Weight gain, weight loss		
Psychiatric disorders		Depressed mood	Anxiety, decreased libido, increased libido
Nervous system disorders	Headache	Dizziness	Migraine
Eye disorders		Visual disturbances	Intolerance to contact lenses
Cardiac disorders		Palpitations	
Gastrointestinal disorders	Abdominal pain, nausea	Dyspepsia	Bloating, vomiting
Skin and subcutaneous tissue disorders	Rash, pruritus	Erythema nodosum, urticaria	Hirsutism, acne
Musculoskeletal and connective tissue disorders			Muscle cramps
Reproductive system and breast disorders	Uterine/vaginal bleeding, including spotting	Breast pain, breast tenderness	Dysmenorrhea, changes in vaginal discharge, premenstrual syndrome, breast enlargement
General disorders and administration site conditions		Edema	Fatigue

The most appropriate MedDRA (version 8.1) term is used to describe a certain reaction and its synonyms and related conditions.

Breast cancer risk

Women who have used the combined estrogen-progestin therapy for more than 5 years have been reported to have a more than 2-fold risk of having breast cancer diagnosed.

The increased risk in women using estrogen alone is lower than that seen in women using combined HRT.

The level of risk is dependent on the duration of therapy (see section 4.4).

Absolute risk estimations based on results of the largest randomized placebo-controlled trial (WHI) and the largest meta-analysis of prospective epidemiological studies are presented below:

Largest meta-analysis of prospective epidemiological studies

Estimated additional risk of breast cancer after 5 years of use in women with body mass index (BMI) of 27 (kg/m^2)

Age at start of HRT (years)	Incidence per 1000 never-users of HRT over a 5-year period (age 50–54 years)*	Risk ratio	Additional cases per 1000 HRT users after 5 years
		Estrogen-only HRT	
50	13.3	1.2	2.7

		Combined estrogen-progestin	
50	13.3	1.6	8.0
* Taken from frequency in England in 2015 in women with BMI 27 (kg/m^2) Note: Since the background frequency of breast cancer varies in EU countries, the number of additional cases of breast cancer will also change proportionately.			

Estimated additional risk of breast cancer after 10 years of use in women with body mass index (BMI) of 27 (kg/m^2)

Age at start of HRT (years)	Incidence per 1000 never-users of HRT over a 10-year period (age 50–59 years)*	Risk ratio	Additional cases per 1000 HRT users after 10 years
		Estrogen-only HRT	
50	26.6	1.3	7.1
		Combined estrogen-progestin	
50	26.6	1.8	20.8
* Taken from frequency in England in 2015 in women with BMI 27 (kg/m^2) Note: Since the background frequency of breast cancer varies in EU countries, the number of additional cases of breast cancer will also change proportionately.			

US WHI studies – increased risk of breast cancer after 5 years of use

Age range (years)	Incidence per 1,000 women in placebo-controlled arm after 5 years of use	Risk ratio and 95% CI	Additional cases per 1,000 women using HRT after 5 years of therapy (95% CI)
		Estrogen-only therapy (conjugated estrogen)	
50–79	21	0.8 (0.7–1.0)	-4 (-6–0)*
		Combination of conjugated estrogen and medroxyprogesterone acetate ‡	
50–79	17	1.2 (1.0–1.5)	+4 (0–9)
‡ When the analysis was restricted to women who had not used HRT prior to the study, no significant increase in risk was observed during the first 5 years of therapy. After 5 years, the risk was increased compared with women who had not used HRT. * WHI study in hysterectomized women, which did not show an increased risk of breast cancer			

Endometrial cancer risk

Postmenopausal women with a uterus

The endometrial cancer risk in women not using HRT is about 5 per 1,000 women. Estrogen-only HRT is not recommended to women with a uterus because it increases the risk of endometrial cancer (see section 4.4).

In epidemiological studies, the increase in the risk of endometrial cancer varied depending on the duration of estrogen replacement therapy and the estrogen dose from 5 to 55 extra cases diagnosed per 1,000 women between the ages of 50 and 65 years.

Adding a progestin to the estrogen therapy for at least 12 days per cycle can prevent this increased risk. In the MWS study, 5 years of combined HRT (sequential or continuous) did not increase the risk of endometrial cancer [RR 1.0 (0.8–1.2)].

Ovarian cancer

Use of estrogen replacement therapy or combined estrogen-progestin therapy 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 a slightly increased overall risk of ovarian cancer in women using HRT compared to women who had never used HRT (RR 1.43, 95% CI 1.31–1.56). In women aged 50 to 54 years taking HRT for 5 years, about one extra case per 2,000 users was detected. In women aged 50 to 54 years who are not taking HRT, about two women in 2,000 were diagnosed with ovarian cancer over a five-year period.

Risk of venous thromboembolism

HRT is associated with a 1.3–3-fold increased relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The risk of such an event is highest during the first year of using hormone therapy (see section 4.4). The results of the WHI studies are presented in the table below:

WHI studies – increased risk of VTE over 5 years of use

Age range (years)	Incidence per 1,000 women in placebo-controlled arm over 5 years	Risk ratio and 95% CI	Additional cases per 1,000 women using HRT
Oral estrogen-only therapy*			
50–59	7	1.2 (0.6–2.4)	1 (-3–10)
Oral combined estrogen-progestin therapy			
50–59	4	2.3 (1.2–4.3)	5 (1–13)
* investigated in women with no uterus			

Risk of coronary artery disease

The risk of coronary artery disease is slightly increased in women over the age of 60 years who are using combined HRT (see section 4.4).

Risk of cerebral infarction

Use of estrogen-only therapy and combined estrogen-progestin therapy is associated with an up to 1.5-fold increased risk of cerebral infarction. The risk of cerebral hemorrhage is not increased during HRT.

This relative risk is not dependent on age or on duration of therapy but as the baseline risk is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age (see section 4.4).

WHI studies – increased risk of cerebral infarction* over 5 years of use

Age range (years)	Incidence per 1,000 women in placebo-controlled arm over 5 years	Risk ratio and 95% CI	Additional cases per 1,000 women using HRT
50–59	8	1.3 (1.1–1.6)	3 (1–5)
* no differentiation was made between cerebral infarction and cerebral hemorrhage			

Other adverse reactions reported in association with estrogen treatment:

- Gall bladder disease
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura

- Possible dementia in women over the age of 65 (see section 4.4)

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose

Overdose may cause nausea and vomiting. Some women may experience breakthrough bleedings. There is no specific antidote, and treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural and semisynthetic estrogens; ATC code G03CA03

Estradiol valerate:

The active substance contained in Progynova tablets is estradiol valerate, which is a prodrug of the synthetic 17ß-estradiol and chemically and biologically identical to endogenous human estradiol. It substitutes for the loss of estrogen production in menopausal women and alleviates menopausal symptoms.

Estrogens prevent the reduction of bone mass during the menopause and after a hysterectomy.

Clinical trial information

Relief of symptoms caused by estrogen deficiency

- Relief of menopausal symptoms was achieved during the first weeks of treatment.

Prevention of osteoporosis

- Estrogen deficiency at menopause is characterized by faster than normal bone metabolism and decline in bone mass.
- The effect of estrogens on bone mineral density is dose-dependent. The protective effect remains for as long as treatment is continued. After discontinuation of HRT, bone mass is lost at a rate similar to that in women not using HRT.
- Evidence from the WHI trial and meta-analyzed trials shows that HRT (estrogen alone or in combination with a progestin) 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. However, the evidence for that is more limited.

The addition of a progestin has not been shown to have an effect on the efficacy of estrogen in the approved indications.

5.2 Pharmacokinetic properties

Absorption

After oral administration estradiol valerate is absorbed quickly and completely. Estradiol valerate is a steroid ester, and it is decomposed into estradiol and valeric acid during the absorption and first-pass hepatic circulation. Estradiol is metabolized concomitantly, transforming, for example, into estrone, estriol and estrone sulfate. The bioavailability of orally administered estradiol valerate is about 3%. Food does not affect the bioavailability of estradiol.

Distribution

The peak serum concentration of estradiol (about 15 pg/ml) is achieved within 4–9 hours of ingesting the tablet. After 24 hours, the serum estradiol concentration is expected to decrease to 8 pg/ml.

Estradiol is bound to albumin and SHBG (sex hormone binding protein). 30–40% of estradiol is bound to SHBG; the unbound fraction is about 1–1.5%.

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

Biotransformation

Following the degradation of the ester bond of exogenous estradiol valerate, metabolism is consistent with the metabolism of endogenous estradiol. Estradiol is metabolized mainly in the liver but also elsewhere, for example, in the intestines, kidneys, skeletal muscles, and target organs. These processes generate estrone, estriol, catechol estrogens and their sulfate and glucuronide conjugates, which are all clearly less estrogenic or even non-estrogenic.

Elimination

The total clearance of estradiol from serum after a single intravenous administration varies greatly from 10 to 30 ml/min/kg. A certain percentage of estradiol metabolites are excreted in bile and undergo so-called enterohepatic pass. Finally, estradiol metabolites are excreted mainly as sulfates and glucuronides in urine.

Steady state

During continuous use of Progynova tablets, serum estradiol concentration is about two times higher than after a single dose. The average estradiol concentration in serum is 15–30 pg/ml. Compared with estradiol, the serum concentration of the less estrogenic metabolite estrone is about 8 times higher and that of estrone sulfate is about 150 times higher. Pre-treatment levels of serum estradiol and estrone concentrations are achieved within 2–3 days after discontinuing the therapy with Progynova.

5.3 Preclinical safety data

The toxicity profile of estradiol is well known. There are no data which could be of relevance to the prescriber that are additional to those already included in other sections.

Carcinogenicity

The systemic tolerance of repeated administration and possible tumorigenic activity have been investigated in animal studies. These tests have not revealed any objections to the use of the preparation at the recommended dosages. However, it should be kept in mind that sex steroids may stimulate the growth of certain hormone-dependent tissues and tumors.

Embryotoxicity/teratogenicity

According to reproductive toxicology studies, estradiol valerate is not teratogenic. Since no non-physiological estradiol concentrations are formed in plasma during treatment with estradiol valerate, the product poses no risk to the fetus.

Mutagenicity

According to *in vitro* and *in vivo* studies with 17β-estradiol, the substance is not mutagenic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core: Lactose monohydrate, maize starch, povidone 25 000, talc, magnesium stearate

Coating (2 mg tablet): Sucrose, povidone 700 000, macrogol 6000, talc, calcium carbonate, montanglycol wax.

6.2 Incompatibilities

None

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Progynova 2 mg tablet:
1 x 20 tablets in blister packs (PVC/aluminum).

6.6 Special precautions for disposal and other handling

Store the medicine appropriately and out of the reach of children.

7. MANUFACTURED BY

Bayer Weimar GmbH und Co. KG

Doebereinestr. 20

99427 Weimar

Germany

8. DATE OF REVISION OF THE TEXT

13 July 2021 Ref :17863