INFORMATION FOR HEALTHCARE PROFESSIONALS

1. NAME OF THE MEDICINAL PRODUCT

Climen® coated tablets 2 mg; 2 mg/1 mg

2. QUALITATIVE AND **QUANTITATIVE** COMPOSITION

Oestradiol valerate, cyproterone acetate

One Climen blister contains 11 white and 10 pink-coloured coated tablets. Each white coated tablet

contains:
Oestradiol valerate 2 mg

Each pink-coloured coated tablet contains:
Oestradiol valerate 2 mg and
Cyproterone acetate 1 mg

Excipients with known effect: 44 mg lactose and 34 mg sucrose (see section 4.4.). For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Coated tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hormone replacement therapy (HRT) for peri- and postmenopausal oestrogen deficiency symptoms.

Prevention of osteoporosis in postmenopausal women with a high fracture risk who show an intolerability or contraindication to other medicinal products authorised for osteoporosis prevention.

Only limited experience is available in the treatment of women over 65 years of age.

4.2 Posology and method of administration

Starting to take Climen

No previous treatment with medicinal products for hormone replacement therapy
Take one unchewed tablet daily with sufficient liquid from the 5th – 25th day of the cycle (1st day of menstruation = 1st day of the cycle).

Amenorrhoeic patients or patients with very irregular periods (exclude pregnancy first; see section 4.6) as well as postmenopausal patients can start any day.

Switching from another medicinal product for hormone replacement therapy
In women being switched from continuous combined hormone replacement therapy, treatment should be initiated on the day after completion of the treatment cycle of the previous therapy. Women being switched from cyclical hormone replacement therapy start taking Climen on the day after the tablet- free interval.

The lowest effective dose should be used for the shortest possible treatment period both when commencing and resuming treatment for postmenopausal symptoms (see also section 4.4).

Posology

Take 1 tablet daily for 21 days unchewed with sufficient liquid. One white tablet is taken daily during the first 11 days, then one pink-coloured tablet every day for 10 days.

Method of administration

As far as possible, the tablets should be taken at the same time of day.

After the first pack has been finished, the patient observes a tablet-free interval of 7 days, during which menstruation-like withdrawal bleeding occurs. The next pack of Climen is started four weeks after tablet-taking commenced, i.e. on the same day of the week, and so forth.

Missed tablets
If the patient forgets to take a tablet at the usual time, this missed tablet should be taken as quickly as possible. If more than 24 hours have passed since the last forgotten tablet, no additional tablet needs to be taken. If the patient forgets to take several tablets, intermenstrual bleeding can occur.

What to do if bleeding does not occur
As the duration of administration increases, bleeding will be increasingly absent during the tablet-free interval. If pregnancy is suspected, tablet-taking must be interrupted until pregnancy can be ruled out.

Additional information regarding special patient groups

Paediatric population
Climen is not indicated for use in children and adolescents.

Elderly patients
There are no data indicating the necessity for dose adjustment in elderly patients.

Patients with impaired hepatic function
Climen has not been specifically studied in patients with impaired hepatic function. Climen is contraindicated in women with severe hepatic disease (see section 4.3). In women with impaired liver function, close monitoring is required and in case of deterioration of liver function values, the use of HRT should be discontinued (see section 4.4).

Patients with impaired renal function
Climen has not been specifically studied in patients with impaired renal function.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1;
- Current or previous breast cancer or suspicion thereof;
- Oestrogen-dependent malignant tumour or suspicion thereof (particularly endometrial carcinoma);
- Undiagnosed bleeding in the genital area;
- Untreated endometrial hyperplasia;

- Previous or current venous thromboembolic diseases (particularly deep vein thrombosis, pulmonary embolism);
- Known thrombophilic diseases (e.g. protein-C, protein-S or antithrombin deficiency; see section 4.4);
- Existing or recent arterial thromboembolic disease (particularly angina pectoris, myocardial infarction, stroke);
- Acute hepatic disease or previous hepatic disease, if the relevant hepatic enzyme levels have not since normalised;
- Porphyria;
- Pregnancy, lactation;
- Menigioma or history of meningioma
- Previous or current hepatic tumours (benign or malignant);
- Severe hypertriglyceridaemia;
- Otosclerosis with aggravation during previous pregnancies.

4.4 Special warnings and precautions for use

HRT should be initiated exclusively for the treatment of postmenopausal symptoms that adversely affect quality of life. For each individual the benefit and risks should be carefully assessed at least once yearly. HRT should be continued only for as long as the benefit outweighs the risks.

Only limited data are available on the risks of HRT in premature menopause. However, as the absolute risk is lower in younger women, the risk-benefit balance might be more favourable in younger women than in older women.

Medical examination/checkups
Before the start or resumption of hormone replacement therapy, the patient's complete personal and family history needs to be documented. The physical examination (including lower abdomen and breast) should be guided by these medical histories and by the contraindications and warnings. Regular checkups are recommended during the treatment; the frequency and type will depend on the woman’s individual risk situation. The women should also be informed which breast changes they should report to the physician (see "Breast cancer" below). The examinations, including imaging techniques such as mammography, should be performed as per current standard screening practices and the clinical necessities of the individual woman.

Patients suffering from prolactinoma require close medical monitoring (including regular measurements of prolactin levels).

Conditions requiring monitoring
Patients should be closely monitored if any of the following conditions are present, have occurred previously and/or have been aggravated during pregnancy or previous hormone treatment. This also applies if any of the conditions or disorders mentioned below occur or worsen in the course of the present hormone replacement therapy with Climen:
- Leiomyoma (uterine myoma) or endometriosis;
- Risk factors for thromboembolisms (see below);
- Risk factors for oestrogen-dependent tumours, e.g. occurrence of breast cancer in first-degree relatives;
- Hypertension;
- Hepatic disease;
- Diabetes mellitus with or without vascular involvement;
- Cholelithiasis;
- Migraine or (severe) headaches;
- Systemic lupus erythematosus (SLE);
- Previous history of endometrial hyperplasia (see below);
- Epilepsy;
- Asthma;
- Otosclerosis;

- Mastopathy and other benign breast diseases;
- Multiple sclerosis;
- Dubin-Johnson or Rotor syndrome (see below);
- Sickle cell anaemia;
- A history of idiopathic jaundice of pregnancy or severe pruritus of pregnancy or herpes gestationis;
- Sydenham's chorea.

Reasons for immediate discontinuation of therapy
Therapy should be discontinued in the case of a contraindication and in the following situations:
- Jaundice or deterioration of hepatic function;
- Significant increase in blood pressure;
- Onset of migraine-like headaches;
- Pregnancy;
- Symptoms of a thrombotic event or a suspicion thereof;
- Increase in epileptic seizures;
- Sudden onset of perception disorders (e.g. visual disorders, auditory disorders).

The potential for a synergistic increase in the risk of thrombosis should be considered in female patients who exhibit a combination of risk factors or a single risk factor that is particularly pronounced. This increased risk may be greater than the cumulative risk posed by the individual factors. Hormone replacement therapy should not be prescribed if the risk-benefit balance is negative.

Endometrial hyperplasia and cancer
In women with an intact uterus, the risk of endometrial hyperplasia and cancer is increased during relatively long-term oestrogen-only therapy. The reported increase in the risk of developing endometrial cancer in users of oestrogen-only therapy ranges from two- to twelve-foldgreater, compared with women without HRT, depending on the duration of use and oestrogen dose levels (see section 4.8). Upon cessation of treatment, the risk may remain elevated for at least 10 years.

Adjuvant cyclic administration of a progestogen for a period of at least 12 days per month or per 28- day cycle, or continuous combined oestrogen-progestogen treatment of women with an intact uterus, offsets the extra risk associated with oestrogen-only therapy.

Regarding sequentially administered medicinal products for hormone replacement therapy with an adjuvant progestogen for 10 days only, it has not been sufficiently demonstrated that endometrial safety obtained with the added progestogen is assured as well as it is with a 12-day adjuvant progestogen.

Breakthrough bleeding and spotting may occur during the first few months of treatment. In the event of frequent, persistent or recurrent irregular bleeding, or if such bleeding occurs at some subsequent time during the course of therapy or persists after the end of treatment, the cause must be investigated and, if necessary, an endometrial biopsy must be performed to exclude endometrial malignancy.

Breast cancer
The overall evidence shows an increased risk of breast cancer in women taking combined oestrogen-progestagen or oestrogen-only HRT, that is dependent on the duration of taking HRT.

Combined oestrogen-progestogen therapy
The randomised placebo-controlled trial, the 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 taking combined oestrogen-progestagen for HRT that becomes apparent after about 3 (1-4) years (see Section 4.8).

Oestrogen-only therapy
The WHI study showed no increased risk of breast cancer in hysterectomised women on oestrogen- only therapy. Observational studies of oestrogen-only therapy have generally reported a small

increased risk of having breast cancer diagnosed that was lower than that found in users of oestrogen-progestogen combinations (see section 4.8).

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, especially combined treatment with oestrogens and progestogens, leads to increased breast density on mammograms, which may have an adverse effect on radiological breast cancer diagnosis.

Ovarian cancer risk
Ovarian cancer is much rarer than breast cancer. Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking oestrogen-only or combined oestrogen-progestogen HRT, which becomes apparent within 5 years of use and diminishes over time after stopping.
Some other studies, including the WHI study, suggest that the use of combined HRT may confer a similar or slightly smaller risk (see section 4.8).

Venous thromboembolism
HRT is associated with a 1.3 to 3-fold increase in the risk of venous thromboembolism (VTE), especially deep vein thrombosis or pulmonary embolism. VTE is more likely to occur during the first year of HRT than later (see section 4.8).

Patients with a history of thrombophilia have an increased risk of VTE. HRT can increase this risk, and is thus contraindicated in these patients (see section 4.3).

Risk factors generally known to be associated with VTE include the use of oestrogens, older age, major surgery, prolonged periods of immobilisation, obesity (BMI > 30 kg/m^2), pregnancy/postpartum period, systemic lupus erythematosus (SLE) and cancer. There is no consensus regarding the possible role varicose veins in VTE.

As in all postoperative patients, prophylactic measures to prevent VTE after surgery must be considered. If a prolonged period of immobilisation is recommended after elective surgery, HRT should be discontinued 4 to 6 weeks prior to the procedure. Treatment should be resumed only when the woman has been completely remobilised.

Women who themselves have no history of VTE can be considered for thrombophilia screening if they have first-degree relatives with a history of VTE at an early age. Before undergoing the screening the patient should be informed about the limited predictive value of this procedure (only some of the defects that cause thrombophilia will be identified). HRT is contraindicated if a thrombophilic defect is identified and there is a family history of thrombosis, or if the identified defect is serious (e.g. antithrombin, protein-S and/or protein-C deficiency or a combination of defects).

Female patients receiving permanent anticoagulant treatment should undergo a careful risk-benefit assessment prior to receiving HRT.

Administration of the medicinal product must be stopped if VTE develops after HRT is started. Patients should be told to contact a physician immediately if they notice possible symptoms indicative of thromboembolism (in particular painful swelling of a leg, sudden onset of chest pain, dyspnoea).

Coronary heart disease
There is no evidence from randomised controlled studies that combined HRT with oestrogen and progestogen or oestrogen-only therapy protects women from myocardial infarction, regardless of whether or not they have coronary heart disease.

Combined oestrogen-progestogen therapy
The relative risk of coronary heart disease is slightly increased on combined HRT with oestrogen and progestogen. As the baseline risk for coronary heart disease is largely age-dependent, the number of

extra cases attributable to HRT with oestrogen and progestogen is very low in premenopausal healthy women. However, the number rises with increasing age.

Oestrogen-only therapy
No evidence of an increased risk of coronary heart disease was found in hysterectomised women on oestrogen-only therapy in randomised controlled studies.

Stroke
Combined treatment with oestrogen and progestogen and oestrogen-only therapy are associated with an up to 1.5-fold increased risk of stroke. The relative risk is irrespective of age and time since menopause. However, as the baseline risk of suffering a stroke is largely age-dependent, the overall risk of stroke for women on HRT rises with increasing age (see section 4.8).

Hepatic tumour
In rare cases, benign, even more rarely malignant, hepatic tumours have been observed after the administration of hormonal active substances such as those contained in hormone replacement therapy products. These tumours have in isolated cases led to life-threatening intra-abdominal haemorrhages. If severe epigastric pain, hepatomegaly or signs of intra-abdominal haemorrhage become evident, a hepatic tumour should be included in the differential diagnosis.

Possible effects on male newborns
Although it is impossible to extrapolate the results of reproductive toxicological animal studies directly to humans, consideration must nevertheless be given to the fact that taking Climen during the hormone-sensitive differentiation phase of the genital organs (approximately from the 45th day of a pregnancy or approximately 59 days after the start of the last withdrawal bleeding) might cause feminisation phenomena in male foetuses. Newborns who were monitored after *in utero* exposure to cyproterone acetate did not show any feminisation phenomena. Nevertheless, pregnancy is a contraindication to the administration of Climen.

The issue of possible teratogenic effects
A possible relationship between the administration of female sex hormones in early pregnancy and the occurrence of deformities is currently the subject of discussion.

These discussions are based on epidemiological investigations consisting of retrospective and prospective studies, with many questions left unanswered. In principle, no conclusions about a causal relationship can be drawn from such investigations, inasmuch as only group differences have been identified, which can also be explained by other factors.

Although the suspicion that a causal relationship might exist between the administration of female sex hormones in early pregnancy and the occurrence of deformities can be regarded as unfounded, it is important to understand that teratogenic effects cannot be excluded with absolute certainty for any medicinal product - including sex hormones. This residual uncertainty is the reason why pregnancy must be ruled out for certain indications before sex hormone therapy is prescribed.

Meningioma
The occurrence of meningiomas (both single and multiple) has been reported in connection with the use of cyproterone acetate, particularly at high doses of 25 mg per day and above and when administered for prolonged periods (see section 5.1). If a patient is diagnosed with meningioma, any medicinal product containing cyproterone acetate, including Climen, must be discontinued by way of precaution.

Hepatitis C
In clinical studies with the combination regimen for hepatitis C virus (HCV), ombitasvir/paritaprevir/ritonavir with or without dasabuvir, an increase in ALT by more than 5 times the upper limit of normal (ULN) occurred significantly more frequently in women using medicinal products containing ethinylestradiol such as CHC. In addition, ALT increases were observed in users of medicinal products containing ethinylestradiol during treatment with glecaprevir/pibrentasvir. The

frequency of elevated ALT values in women using medicinal products with oestrogens other than ethinylestradiol, such as estradiol, was similar in those who received no oestrogens. Since the number of women using these other oestrogens is limited, caution is nevertheless advised with simultaneous administration with the combination regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir and also with the regimen glecaprevir/pibrentasvir. See section 4.5.

Other pathological conditions

- Estrogens can cause fluid retention; patients with cardiac or renal dysfunction must therefore undergo careful observation. Patients with terminal renal insufficiency must be monitored closely, as increased plasma levels of the circulating active substances in Climen must be assumed.
- Women with pre-existing hypertriglyceridaemia must be closely monitored during oestrogen or oestrogen/progestogen hormone replacement therapy; this is because rare cases of a strong increase in plasma triglycerides with resulting pancreatitis have been reported to occur in similar circumstances in association with oestrogen therapy.
- Oestrogens increase the concentration of thyroxine-binding globulin (TBG), resulting in an increase in the total circulating thyroid hormone, which is measured by means of the protein- bound iodine (PBI), the T4 level (by means of column separation or by radioimmunoassay) or the T3 level (radioimmunoassay). The T3 resin uptake is reduced, reflecting an increase in TBG. The concentrations of free T4 and T3 do not change. Other binding proteins may be increased in the serum, such as corticosteroid-binding globulin (CBG) and sex hormone-binding globulin (SHBG), which leads to an increase in the circulating corticosteroids and sex hormones. Free or bioactive hormone concentrations remain unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha 1-antitrypsin, ceruloplasmin).
- Cognitive skills do not improve with HRT. There is no evidence of an increased risk of probable dementia in women who were over 65 years of age at the start of continuous combined HRT or oestrogen-only therapy.
- Uterine leiomyomas (myomas) can increase in size under the influence of oestrogens. If such growth is ascertained, the treatment should be discontinued. If endometriosis recurs during treatment, it is recommended that the treatment be discontinued.
- It is known that oestrogens promote the formation of gallstones. Some women have a tendency to develop gallbladder disease during oestrogen therapy.
- Chloasma can occasionally occur, particularly in women with a history of chloasma gravidarum. Women with this tendency should therefore not directly expose themselves to the sun or ultraviolet light during hormone replacement therapy.
- Climen is not intended for contraception. Non-hormonal methods (except the Knaus-Ogino calendar method and the temperature method) should be used for contraception if necessary.
- Exogenous oestrogens may cause or aggravate symptoms of hereditary or acquired angioedema.

Climen does not protect against HIV.

Patients with rare hereditary galactose intolerance, rare hereditary fructose intolerance, glucose- galactose malabsorption, lactase deficiency or sucrase-isomaltase deficiency should not take Climen.

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 Climen

Substances increasing the clearance of sex hormones (diminished efficacy by enzyme-induction) e.g.: The metabolism of oestrogens and progestogens can be potentiated by the simultaneous administration of substances which induce drug-metabolising enzymes, especially cytochrome P450 enzymes; these substances include anticonvulsants (e.g. barbiturates, phenytoin, primidone, carbamazepine) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz) and possibly also felbamate, griseofulvin,

oxcarbazepine, topiramate and herbal medicinal products containing St. John's Wort (*hypericum perforatum*).

Clinically, increased oestrogen and progestogen metabolism can attenuate the effect of these hormones and result in changes to uterine bleeding patterns.

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

Therefore, the prescribing information of concomitant HIV/HCV medications should be consulted to identify potential interactions and any related recommendations.

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 oestrogen or the progestin or both.

In rare cases, decreased oestradiol levels have been observed in the context of the simultaneous use of certain antibiotics (e.g. penicillins and tetracyclines).

Other substances such as paracetamol that are strongly conjugated during intestinal passage can act as a competitor in the oestrogen conjugation process, thereby bringing about increased oestradiol availability.

The influence on glucose tolerance may alter the need for oral antidiabetics or insulin. Other interactions
In clinical studies with the combination regimen for HCV, ombitasvir/paritaprevir/ritonavir with or without dasabuvir, an increase in ALT by more than 5 times the upper limit of normal (ULN) occurred significantly more frequently in women using medicinal products containing ethinylestradiol such as CHC. The frequency of elevated ALT values in women using medicinal products with oestrogens other than ethinylestradiol, such as estradiol, was similar to that in those who received no oestrogens. Since the number of women using these other oestrogens is limited, caution is nevertheless advised with simultaneous administration of the combination regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir and also with the regimen glecaprevir/pibrentasvir (see section 4.4).

Other forms of interaction Laboratory tests
The use of sex hormones can influence the results of certain laboratory tests, including the biochemical parameters of hepatic, thyroid, adrenal and renal function and the plasma levels of (carrier) proteins, e.g. of corticosteroid-binding globulin and of lipid/lipoprotein fractions, the parameters of carbohydrate metabolism and the parameters of clotting and fibrinolysis. Changes generally remain within the normal reference range (for further information, see section 4.4 “Other pathological conditions”).

4.6 Pregnancy and lactation

Pregnancy
Climen is not indicated during pregnancy. Pregnancy must be ruled out before starting Climen. If pregnancy occurs during treatment with Climen, the treatment should be discontinued immediately.

Only very limited clinical data, which thus far have not indicated any undesirable effects, are available as regards the use of cyproterone acetate in pregnant patients. The administration of cyproterone acetate during the hormone-sensitive differentiation phase of the genital organs (approximately from day 45 of pregnancy) could cause feminisation in male foetuses after high doses. Animal studies have revealed reproductive toxicity (see section 5.3).

The majority of currently available epidemiological studies of relevance with regard to inadvertent foetal exposure to combinations of oestrogens and progestogens show no teratogenic or foetotoxic effects.

Breastfeeding
Climen is not indicated during breastfeeding. Small amounts of sex hormones are excreted in human milk.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. No effects on the ability to drive and use machines have been observed in women using Climen.

4.8 Undesirable effects

The following adverse reactions, for which a connection with Climen has been neither confirmed nor refuted, have been reported in users of hormone replacement therapy (post-marketing data).

The following categories are used for expressing the frequency of undesirable effects: Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10) Uncommon (≥ 1/1,000 to < 1/100) Rare (≥ 1/10,000 to < 1/1,000) Very rare (< 1/10,000)
Not known (cannot be estimated from the available data)

System organ class	**Common ADRs ≥ 1/100 to < 1/10**	**Uncommon ADRs ≥ 1/1,000 to < 1/100**	**Rare ADRs ≥ 1/10,000 to < 1/1,000**
Immune system disorders		Hypersensitivity reactions	
Metabolism and nutrition disorders	Changes in body weight		
Psychiatric disorders		Depressed mood	Anxiety state, altered libido
Nervous system disorders	Headache	Dizziness	Migraine
Eye disorders		Visual disturbances	Contact lens intolerability
Cardiac disorders		Palpitations	
Gastrointestinal disorders	Abdominal pain, nausea	Dyspepsia	Flatulence, vomiting
Skin and subcutaneous tissue disorders	Exanthema, pruritus	Erythema nodosum, urticaria	Hirsutism, acne
Musculoskeletal and connective tissue disorders			Muscle cramps
System organ class	**Common ADRs ≥ 1/100 to < 1/10**	**Uncommon ADRs ≥ 1/1,000 to < 1/100**	**Rare ADRs ≥ 1/10,000 to < 1/1,000**

Reproductive system and breast disorders	Changes in menstrual bleeding pattern, increased or attenuated withdrawal bleeding, intermenstrual bleeding in the form of spotting or even breakthrough bleeding (these bleeding irregularities usually resolve with continued therapy).	Breast pain, breast tension	Dysmenorrhoea, changes in vaginal secretion, symptoms similar to premenstrual syndrome, breast enlargement
General disorders and administration site conditions		Oedema	Fatigue

The most appropriate MedDRA term (version 8.0) to describe a certain adverse reaction is listed. Synonyms and associated conditions are not listed but should also be considered.

Breast cancer

The risk of breast cancer diagnosis was increased up to 2-fold in women using combined oestrogen-progestogen therapy for more than 5 years.
The increased risk is lower in users of oestrogen-only therapy than in users of oestrogen-progestogen combination products.
The extent of the risk depends on the duration of use (see section 4.4).

Absolute risk estimations based on results of the largest randomised, placebo-controlled study (WHI study) 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' use in women with BMI 27 (kg/m²)

Age at the start of HRT (years)	**Incidence per 1,000 never-users of HRT over a 5-year period (50-54 years)***	**Relative risk#**	**Additional cases per 1,000 HRT users after 5 years**
Oestrogen-only therapy			
50	13.3	1.2	2.7
Oestrogen-progestogen combination therapy			
50	13.3	1.6	8.0
* Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m²) # Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.			

Estimated additional risk of breast cancer after 10 years' use in women with BMI 27 (kg/m²)

Age at the start of HRT (years)	**Incidence per 1,000 never-users of HRT over a 10-year period (50-59 years)***	**Relative risk#**	**Additional cases per 1,000 HRT users after 10 years**
Oestrogen-only therapy			
50	26.6	1.3	7.1
Oestrogen-progestogen combination therapy			
50	26.6	1.8	20.8

* Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m^2) # Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.

WHI studies in the US – excess breast cancer risk after 5 years of HRT

Age group (years)	**Incidence in 1,000 women in the placebo arm over a 5-year period**	**Relative risk (95% CI)**	**Additional cases per 1,000 HRT users over a 5-year period (95% CI)**
Oestrogen-only therapy (CEO)			
50 - 79	21	0.8 (0.7 - 1.0)	-4 (-6 - 0)*
Oestrogen & progestogen (CEO + MPA)#			
50 - 79	17	1.2 (1.0 - 1.5)	+4 (0 - 9)
CEO: conjugated equine oestrogens; MPA: medroxyprogesterone acetate * WHI study in women without a uterus, which showed no increased breast cancer risk. # When analysis was restricted to women who had not used HRT before the study, the risk did not appear to be increased during the first 5 years of treatment: After 5 years, the risk was higher than in untreated women.			

Endometrial cancer:

Postmenopausal women with an intact uterus
Approximately 5 out of 1,000 women with an intact uterus who do not use HRT develop endometrial cancer.

The use of oestrogen-only therapy is not recommended in women with an intact uterus, as this increases the risk of endometrial cancer (see section 4.4).

Depending on the duration of oestrogen-only therapy and the oestrogen dose, the increased risk of endometrial cancer in epidemiological studies was 5 to 55 additionally diagnosed cases per 1,000 women between 50 and 65 years of age.

This increased risk can be avoided by adding a progestogen to oestrogen-only therapy for at least 12 days per cycle. In the Million Women Study, the risk of endometrial cancer was not increased after 5 years of using combined HRT (sequentially or continuously) (RR 1.0 (95% CI 0.8 - 1.2)).

Ovarian cancer risk
The use of oestrogen-only or combined oestrogen-progestogen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see section 4.4).
A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using HRT compared to women who have never used HRT (RR 1.43, 95% CI 1.31 - 1.56). For women aged 50 to 54 years taking HRT for 5 years, this results in 1 extra case per 2,000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2,000 will be diagnosed with ovarian cancer over a 5-year period.

Venous thromboembolism
The risk of venous thromboembolism (VTE), e.g. deep leg vein or pelvic vein thrombosis or a pulmonary embolism, is 1.3-3 times higher with HRT. Occurrence of such an event is more likely during the first year of treatment than in the subsequent years of treatment (see section 4.4). The relevant results from the WHI studies are presented in the following section:

WHI studies – extra risk of VTE after 5 years of HRT

Age group (years)	Incidence per 1,000 women in the placebo arm over a 5-year period	Relative risk (95% CI)	Additional cases per 1,000 HRT users after 5 years
Oral oestrogen-only therapy*			
50 - 59	7	1.2 (0.6 - 2.4)	1 (-3 - 10)
Combined oral oestrogen-progestogen therapy			
50 - 59	4	2.3 (1.2 - 4.3)	5 (1 - 13)

* Study in women without a uterus Coronary heart disease

The risk of developing coronary heart disease is slightly increased in combined oestrogen-progestogen HRT users over 60 years of age (see section 4.4).

Stroke

The use of oestrogen-only therapy or combined oestrogen-progestogen therapy is associated with up to a 1.5-fold increased risk of ischaemic stroke. The risk of haemorrhagic stroke is not increased with HRT.

This relative risk is not dependent on age or duration of use. However, as the baseline risk is heavily dependent on age, the overall risk is increased with increasing age in women on HRT (see section 4.4).

Combined WHI studies – additional risk of ischaemic stroke* after 5 years of HRT

Age group (years)	Incidence per 1,000 women in the placebo arm over a 5-year period	Relative risk (95% CI)	Additional cases in 1,000 HRT users over 5 years
50 - 59	8	1.3 (1.1 - 1.6)	3 (1 - 5)

* No distinction was made between ischaemic and haemorrhagic stroke. What to do if intermenstrual bleeding occurs

For women receiving replacement therapy, any recurrent intermenstrual bleeding should be investigated diagnostically (see endometrial hyperplasia, section 4.4). Climen should be continued during intermenstrual bleeding in order to avoid more intense withdrawal bleeding. Additional oestrogen can be administered for 4 to 5 days in an attempt to stop the intermenstrual bleeding.

However, an exhaustive gynaecological examination and possible curettage are indicated if intermenstrual bleeding cannot be stopped despite this additional therapy, or if several successive cycles occur at irregular intervals or occur for the first time after prolonged administration of Climen. In these cases it is improbable that the irregular bleeding can be attributed to the medicinal product, as these occurrences are mostly due to organic causes (e.g. submucous myomas, polyps) (see also section 4.4).

Hepatic tumour

In rare cases, benign − and even more rarely − malignant hepatic tumours have been observed after use of hormonal active substances such as those contained in Climen; in isolated cases, these have led to life-threatening intra-abdominal haemorrhages. If severe epigastric pain, hepatomegaly or signs of intra-abdominal haemorrhage occur, the possibility of a hepatic tumour should be included in the differential diagnosis (see also section 4.4).

Carbohydrate metabolism

Depending on the type and quantities of the active substances contained in this oestrogen/progestogen combination preparation, it may cause an exaggerated glucose and plasma insulin response (decreased glucose tolerance) especially with oral glucose challenge. As the influence on carbohydrate metabolism cannot be predicted, women with diabetes mellitus should be carefully monitored. The need for insulin or oral antidiabetics may be either increased or decreased (see also sections 4.4 and 4.5).

Influence on normal clinical chemistry values

The erythrocyte sedimentation rate may increase in the absence of disease. This may occur due to shifts in the individual plasma protein fractions. An increase in serum copper and serum iron levels as well as in alkaline leukocyte phosphatase has also been described.

Other adverse drug reactions have also been reported in connection with oestrogen/progestogen treatment:
- Gallbladder disease;
- Skin and subcutaneous tissue disorders: chloasma, erythema multiforme, vascular purpura, eczema, hair loss;
- Probable dementia in women over 65 years of age (see section 4.4);
- Increase in appetite.

Exogenously administered oestrogens can trigger or worsen symptoms of angioedema in women with hereditary angioedema (see section 4.4).

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

Saudi Arabia:
The National Pharmacovigilance Centre (NPC).
SFDA call center: 19999.
Email: npc.drug@sfda.gov.sa.
Website: https://ade.sfda.gov.sa

Other Countries:
Please contact the relevant competent authority

4.9 Overdose

Overdose may, in some women, lead to nausea and vomiting and to withdrawal bleeding. There are no specific antidotes and treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiandrogens and oestrogens, ATC code: G03HB01

Climen contains the oestrogen oestradiol valerate, a prodrug of 17β-oestradiol. The active substance, synthetic 17β-oestradiol, is chemically and biologically identical to endogenous human oestradiol. It replaces the loss of oestrogen production in menopausal women and relieves associated symptoms.

Oestrogens prevent postmenopausal or post-ovariectomy loss of bone mass.

Cyproterone acetate, which is added in the 2nd phase of treatment, is a synthetic hydroxyprogesterone derivative with progestogenic, antigonadotropic and antiandrogenic properties.

As oestrogens promote endometrial growth, unopposed oestrogen administration increases the risk of endometrial hyperplasia and cancer. The addition of a progestogen significantly reduces the oestrogen- related risk of endometrial hyperplasia in women who have not had a hysterectomy.

Meningioma
Based on a French epidemiological cohort study, a cumulative, dose-dependent relationship between cyproterone acetate and meningiomas was observed. This study was based on data from the French

[1] The German Federal Institute for Drugs and Medical Devices
[2] Department of Pharmacovigilance

health insurance (CNAM) and comprised a population of 253,777 women who took 50-100 mg cyproterone tablets. The incidence of menigioma treated by means of surgery or radiation therapy was compared between women exposed to high doses of cyproterone acetate (cumulative dose ≥ 3g) and women who were merely exposed to low doses of cyproterone acetate (cumulative dose < 3g). A relationship between the cumulative dose and the rate of occurrence was demonstrated.

Cumulative dose of cyproterone acetate	***Incidence rate (in patient-years)***	***HR_{adj} (95% CI)[a]***
Minor exposure (<3 g)	***4.5/100.000***	***Ref.***
Exposure to ≥3 g	***23.8/100.000***	***6.6 [4.0-11.1]***
12 to 36 g	***26/100.000***	***6.4 [3.6-11.5]***
36 to 60 g	***54.4/100.000***	***11.3 [5.8-22.2]***
more than 60 g	***129.1/100.000***	***21.7 [10.8-43.5]***

[a] **Adjusted according to age as time-dependent variable and oestrogen at start of administration**

A cumulative dose of for instance 12 g may be equivalent to a year of treatment with 50 mg/day for 20 days per month.

Osteoporosis prevention

- Oestrogen deficiency in the menopause is associated with increased bone turnover and loss of bone mass.
- The effect of oestrogens on bone density is dose-dependent. Protection appears to be effective for as long as the treatment is continued. After discontinuation of HRT, loss of bone mass is comparable to that of untreated women.
- The WHI study and meta-analyses of other studies show that current use of HRT, alone or in combination with a progestogen, reduces the risk of hip, vertebral and other osteoporotic fractures in predominantly healthy women. HRT might also prevent fractures in women with low bone density and/or confirmed osteoporosis, but there are only limited findings available in this regard.

5.2 Pharmacokinetic properties

Cyproterone acetate and oestradiol valerate are rapidly and completely absorbed after oral administration. Natural oestradiol is formed from oestradiol valerate during the absorption phase and the first liver passage. Both active substances reach peak plasma levels after 1 - 3 hours. Oestrogen levels are markedly elevated for approximately 24 hours. Cyproterone acetate concentrations decrease in a biphasic manner with half-lives of 3 - 4 hours and 2 - 4 days. With repeated daily administration, no increase in minimum plasma levels is to be expected for oestradiol, while a 2- to 4-fold increase in minimum plasma levels can be expected for cyproterone acetate.

The two active substances are excreted mainly in metabolised form: for cyproterone acetate 30% via the kidneys and 70% via the liver with a half-life of 2 days, for oestradiol 90% via the urine and 10% via the stools, with a half-life of 1 day.

Bioavailability

Cyproterone acetate is completely bioavailable following oral administration. The bioavailability of oestradiol, after complete cleavage from oestradiol valerate, is approximately 3 %.

5.3 Preclinical safety data

Due to the marked differences between individual laboratory animal species and in relation to humans, the results obtained from animal studies with oestrogens and progestogens remain limited in terms of their predictive value in humans.

Women are particularly exposed to high oestrogen and progestogen concentrations during pregnancy, without experiencing toxic symptoms.

Acute and chronic toxicity
The acute toxicity of oestradiol valerate and cyproterone acetate after oral ingestion is low.

The toxicity profile of oestradiol valerate is well-known. There are no relevant preclinical data for physicians other than the safety information already provided in other sections.

A number of findings from toxicity studies after repeated administration of oestradiol valerate and other oestrogens are available – including increased mortality, haematological disorders, decreased gonad weight, pituitary tumours. Past experience shows that these results have no predictive value in clinical therapy.

Studies of toxicity following repeated administration of high doses of cyproterone acetate in rats, dogs, and monkeys have reported effects that are similar to those described after other progestogens, especially atrophic changes in the gonads and changes in hormonal regulation. Haematological changes and increases in hepatic enzymes were observed in rats and dogs. Hepatic cell hypertrophy and prolactin increases were ascertained in the monkey.

Non-clinical data on cyproterone acetate reveal no special hazard for humans based on conventional studies of repeated dose toxicity.

No qualitatively new effects were noted for the combination consisting of ethinylestradiol and cyproterone acetate; no studies of repeated dose toxicity were carried out using the oestradiol valerate / cyproterone acetate combination.

Animal studies to detect a possible sensitising effect of oestradiol valerate and cyproterone acetate have not been conducted. Many years of clinical experience point to only very isolated cases of suspected allergic reactions; a sensitising effect could not be unequivocally demonstrated.

Reproductive toxicity
Oestradiol valerate possesses an embryolethal effect when administered subcutaneously or intramuscularly, even at a relatively low dose. Embryotoxic effects (growth retardation) have been observed in rats. Deformities of the urogenital tract after administration of oestradiol to rats on day 19 p.c. have likewise been reported. Vaginal and/or uterine tumours developed later in mice after post-partum subcutaneous administration of oestradiol.

Cyproterone acetate caused abnormalities in the male gonads after prenatal exposure (feminisation) in rats, rabbits, dogs and guinea pigs. Embryotoxic, embryolethal and/or teratogenic effects occurred in mice after single cyproterone acetate doses before and during the organogenesis phase. Malformations of the kidneys, lungs and hard palate have been reported.

The administration of cyproterone acetate during the hormone-sensitive differentiation phase of the genital organs led to feminisation signs in the male foetus when given in high doses. No studies of reproductive toxicity using the combination of both active substances have been conducted.

Mutagenic and tumorigenic potential
Most of the mutagenicity studies of oestradiol have been negative. A few studies have indicated induction of chromosomal mutations (aneuploid and structural changes) when administered in high concentrations. Oestradiol induced cell transformations in the context of *in vitro* studies to detect carcinogenic effects. It is unclear to what extent these effects may contribute to the tumorigenicity observed in animal studies. Testing of cyproterone acetate on the basis of a recognised standard battery of tests produced no evidence of mutagenic action. However, in further studies, cyproterone acetate resulted in DNA adduct formation (and an increase in repair synthesis) in rat, monkey and human hepatic cells. This DNA adduct formation was observed under exposure conditions that could occur at the recommended

therapeutic dose. One result of *in vivo* treatment was an increased incidence of focal, possibly preneoplastic hepatic cell foci with modified enzyme expression in female rats, and an increased mutation frequency in transgenic rats carrying a bacterial gene as a mutation marker.

The clinical significance of these findings is unclear at the present time. Previous clinical experience and carefully conducted epidemiological studies do not indicate an increased incidence of hepatic tumours in humans.

Studies of tumorigenicity in rodents did not in principle yield any findings for cyproterone acetate that were different to those obtained with other steroid hormones. Nevertheless, it should be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumours.

In 2-year studies with oral administrations of oestradiol valerate, an increase in pituitary adenomas and benign and malignant breast tumours was observed in rats.

Oestradiol and its esters generally increase the incidence of pituitary and breast tumours in rats and mice, renal tumours in hamsters, and urogenital, testicular and lymphoid tumours in mice. A promoting effect on chemically induced hepatic tumours has likewise been found in animal studies in conjunction with oestradiol esters.

Oestrogen/progestogen combinations appear to have a different effect on tumour development in humans, with most experience being documented in the context of oral contraceptive use. Even though, based on current knowledge, the incidence of ovarian carcinomas, endometrial carcinomas and benign breast tumours in oral contraceptive users is decreasing, there is an increased risk of developing generally rare benign and malignant hepatic tumours, and possibly an increased risk of cervical carcinomas and dysplasias. Moreover, particularly women who started taking oral contraceptives at an early age and continued to take them for a prolonged time, may have a higher probability of developing breast cancer before reaching menopause. The clinical relevance of the preclinical findings is currently unclear. Based on clinical experience, no increase in the occurrence of hepatic tumours is deducible for combinations of ethinylestradiol and cyproterone acetate compared with oral contraceptives.

No studies of tumorigenic potential are known to have been conducted using the combination of oestradiol valerate and cyproterone acetate. The rationale for combining oestradiol valerate with cyproterone acetate is essentially to prevent an increase in endometrial carcinomas occurring in the context of oestrogen-only replacement. The prolonged administration of oestrogens may be associated with an increased risk of breast cancer.

On the whole, the available data do not contraindicate the use of Climen in humans as long as it is administered in accordance with the guidelines pertaining to the stated indications and in the recommended dosage.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, cornstarch, povidone K 25, povidone K 90, talc, magnesium stearate, sucrose, macrogol 6000, calcium carbonate (E 170), titanium dioxide (E 171), yellow iron oxide (E 172), red iron oxide (E 172), glycerol 85% (E 422) and glycol montanate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Blister pack (polyvinyl chloride/aluminium) containing 11 white and 10 pink-coloured coated tablets.
Calendar pack containing
21 coated tablets
3 x 21 coated tablets

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bayer AG
Kaiser-Wilhelm-Allee 1
51368 Leverkusen, Germany.

8. MARKETING AUTHORISATION NUMBER(S)

24211.00.00

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 December 1995 Date of latest renewal: 12 June 2013

10. DATE OF REVISION OF THE TEXT

August 2023

11. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription