PRODUCT INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

ESTRAMON UNO 50 µg/24 hours, Transdermal Patch ESTRAMON UNO 75 µg/24 hours, Transdermal Patch ESTRAMON UNO 100 µg/24 hours, Transdermal Patch

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ESTRAMON UNO 50
1 transdermal patch (matrix system) with 20 cm2 contains:
4.13 mg estradiol hemihydrate equivalent to 4 mg estradiol. Average estradiol release per day: 50 micrograms

ESTRAMON UNO 75
1 transdermal patch (matrix system) with 30 cm2 contains:
6.198 mg estradiol hemihydrate equivalent to 6 mg estradiol. Average estradiol release per day: 75 micrograms

ESTRAMON UNO 100
1 transdermal patch (matrix system) with 40 cm2 contains:
8.26 mg estradiol hemihydrate equivalent to 8 mg estradiol. Average estradiol release per day: 100 Microgram

Other Components with known effect: Soybean oil (Ph.Eur.)

Complete listing of other components see section 6.1.

3. PHARMACEUTICAL FORM

Transdermal patch

Transparent oval patch, consisting of a slit protective film (to be removed before applying thepatch ) and functional layers: a estradiol-containing self-adhesive matrix layer and a waterproof backing film.

4. CLINICAL INFORMATION

4.1 Indications

Hormone replacement therapy (HRT) for estrogen deficiency symptoms after menopause. HRT in estrogen deficiency symptoms in women, whose last menstrual period at least 12 months ago.

Prevention of osteoporosis in postmenopausal women with high Fracture risk, the a intolerance or contraindication to other for osteoporosis prevention approved medicines have (see also section 4.4).

There are only limited experience in the treatment of women over 65 years before.

4.2 Dosage and method of administration

Dosage
The transdermal patch is once weekly, i.e. every 7 days, changed.

Estrogen deficiency symptoms
ESTRAMON UNO is in 3 strengths available: 50, 75 and 100. Both for the start as also for the continuation of a treatment postmenopausal symptoms is the lowest effective dose for the shortest possible duration of therapy to be used (see also section 4.4).

Depending on clinical response the dose can be adjusted to the individual needs of the patient adapted. If themselves after 3 months treatment the symptoms not sufficiently improved have, can the dose increased be. If themselves Symptoms of overdose show (e.g. breast tension), the dose must be reduced ..

of osteoporosis in postmenopausal women For this
is ESTRAMON UNO in 3 ESTRAMON UNO in 3 Strengths available: 50, 75 and 100. The treatment must with a patch Estradiol 50 µg/24 hours started be.
Dose adjustments can under use of Estradiol 50, - 75 and - 100 µg/24 hours patches occur.

General information
ESTRAMON UNO can both cyclically and also continuously be used become.

In women with an intact uterus must regardless of the chosen regime of estrogen treatment with a progestogen, which for the application with a Estrogen approved is, over at least 12-14 days per 28-day cycle combined be, to reduce Estrogen-induced endometrial hyperplasia largely to reduce.
In hysterectomized women is the addition of a progestogen not recommended, except in cases, in which an endometriosis diagnosed was.

Variants of the estrogen monotherapy or. combined estrogen/progestogen therapy
Cyclic or. cyclic sequential
Cyclic application of estrogen with a treatment-free interval, whereby usually on 21 days the application occurs and 7 days application-free are. In women with uterus is additionally sequential a progestogen in the last 12-14 days of therapy supplemented.

Continuous or. continuously sequential
Continuous application of estrogen. In women with uterus additionally sequential a progestogen on 12-14 days of each 28-day cycle.

As progestogen addition can e.g. norethisterone, norethisterone acetate, medroxyprogesterone acetate or progesterone be used are (for further information see professional- and package leaflet of the individual products).

A continuous, non-cyclical treatment can can in hysterectomized women performed be or if during the treatment-free period the symptoms of estrogen deficiency again significantly appear occur.

Type of application

ESTRAMON UNO is applied with its adhesive layer to a clean and dry area of the abdomenapplied . ESTRAMON UNO must not be applied to the breasts in whose proximity applied be.

ESTRAMON UNO is once weekly changed. It must not twice in succession on the same skin area applied be. The skin site should be free of oil and without skin damage or skin irritation be. The waist should be avoided , astight clothing Clothing the patch remove can.

The touching of the adhesive surface should be avoided ..

1. transdermal patches are individually packaged .. Immediately before the application is the packaging at the incision beside the pouch corner torn open and the transdermal patch removed, without it to damage.
2. The transdermal patch is carefully at the perforation up and down bent , untilthe release liner along the along the slit line from the adhesive surface of the transdermal patch detaches. A part of the release liner is removed from the transdermal patch.
3. The exposed become adhesive surface is on a healthy, cleaned skin area applied.
4. The other part of the transdermal patch is gently lifted, so that the remaining part of the release liner removed and the transdermal patch completely applied can be.
5. After the application should the transdermal patch approximately 10 seconds with the flat hand firmly pressed be.

With each new transdermal patch is the Hip side changed.

The transdermal patch should not be direct sunlight exposed be. The transdermal patch adheres even during bathing and Showering or during physical activity well on the skin.

If a transdermal patch prematurely ( beforeexpiration of 7 days )) partially or completely from the skin detach, should it by a new patch replaced be.
After every 7 days is the used patch by a new replaced.

Start of therapy
In postmenopausal women who currently no estrogentreatment, an estrogen monotherapy or a continuously combined HRT receive, can the treatment with ESTRAMON UNO at any desired time started be.

Women who currently a sequential Estrogen-progestogen-therapy receive, should the current treatment cycle complete, before starting the ESTRAMON UNO-treatment begun is. The first day after completion of the previous treatment (with continuous use) or. the first day after the treatment break (in cyclical use) represents a suitable time for the start of a new treatment cycle with ESTRAMON UNO ..

Was the Application of a transdermal patch forgotten, should it as soon as possible be made up . Thenext patch change should according to the the original treatment regimen conducted be. A treatment interruption could the probability of recurrence of symptoms increase and discontinuation- or spotting cause.

4.3 Contraindications

- existing or previous breast cancer or. a corresponding suspicion
- estrogen-dependent malignant tumor or. a corresponding suspicion (before all endometrial carcinoma)
- not clarified bleeding in genital area
- untreated endometrial hyperplasia
- previous or existing venous thromboembolic diseases (especially all deep venous thrombosis, pulmonary embolism)
- known thrombophilic disorders (e.g., protein C, protein S or antithrombindeficiency, see section 4.4)
- existing or recently short Time previous arterial thromboembolic diseases (especially in angina pectoris, myocardial infarction)
- acute liver disease or previous liver diseases, as long as it the relevant liver enzyme levels not normalized have
- porphyria
- known hypersensitivity to the active substance, soy, peanut or a of the in section 6.1 mentioned other components

4.4 Special warnings and precautions for the use

HRT should only for treatment of postmenopausal symptoms initiated be, which the quality of life impair. Benefits and risks should in each individual case at least annually carefully weighed against each other be . An HRT. An HRT should only so long continued be, as the benefit outweighs the risks outweighs.

There are only limited data on Evaluation of the risks of a HRT in premature menopause before. Since however the absolute risk in younger women is lower is, could the benefit-risk ratio in younger women more favorable be than in older.

Medical examination/follow-up examinations
Before starting or resuming a Hormone replacement therapy is a complete personal and family history of the patient to be taken. The physical examination (including abdomen and breast) should themselves on these medical histories as well as the contraindications and warnings orient.

During the treatment are regular check-ups recommended, which themselves in Frequency and type according to the individual risk situation of the woman be directed. The women should be informed about ,which changes of the breasts they she the doctor inform must (see section "breast cancer" further below).

The examinations, including imaging procedures such as Mammography, are according to the currently usual preventive practice and the clinical necessities of the individual woman to be performed.

Situations, that require monitoring require
The patients should be closely monitored ,if a of the following situations or .. is present or was previously present or. itself during a pregnancy or a previous hormone treatment worsened has. This also applies also to the case, that a of the following mentioned Situations or diseases during

the course of the current hormone replacement therapy with ESTRAMON UNO occurs or. worsens deteriorated:

- ( uterine myoma)) or Endometriosis
- Risk factors for thromboembolisms (see below)
- Risk factors for estrogen-dependent tumors, e.g. occurrence of breast cancer in first-degree relatives 1. Degrees
- Hypertension
- Liver diseases (e.g. Liver adenoma)
- Diabetes mellitus with or without involvement of the vessels
- Cholelithiasis
- Migraine or (severe) headaches
- systemic Lupus erythematosus (SLE)
- Endometrial hyperplasia in the medical history (see below)
- Epilepsy
- Asthma
- Otosclerosis

Reasons for an immediate discontinuation of therapy:
The Therapy is in the presence of a contraindication as well as in the following situations to be discontinued:

- Jaundice or deterioration of liver function
- significant increase of the Blood pressure
- Insertion migraine-like Headaches
- Pregnancy

Endometrial hyperplasia and -cancer
In women with intact uterus is the risk for endometrial hyperplasia and -carcinoma in long-term Estrogen- monotherapy increases. The reported increase of the risk for the development of endometrial carcinoma in users of Estrogen-monotherapy varies between a twofold to twelvefold increase, compared with women without HRT, depending on the duration of use and the level of estrogen dose (see section 4.8). After completion of the treatment can the risk for at least 10 years remain increased.

The additional cyclical administration a progestogen for the duration of at least 12 days per month or. per 28-day cycle or the continuous combined estrogen-progestogen-treatment of women with intact Uterus compensates the additional risk, which arises from estrogenmonotherapy ..

ESTRAMON UNO 75 and ESTRAMON UNO 100 ESTRAMON UNO 75 and ESTRAMON UNO 100 has not been shown, that the endometrial Safety through addition of a progestogen ensured is.

Breakthrough- and spotting may during the first months of treatment occur. If such bleeding some time later in the course of the therapy occur or persist after end of therapy, the cause must be determined and if necessary a biopsy of the endometrium performed be, to a malignant disease of the endometrium exclude.

Unopposed estrogen stimulation can lead to a premalignant or malignant Transformation residual endometriosis lesions lead. Therefore should in consideration be taken , in thecases a progestin additionally to estrogen replacement therapy Estrogen replacement therapy to give, in which due to an endometriosis a hysterectomy performed was and in which a residual endometriosis exists.

breast cancer
It gives evidence for an increased breast cancer risk in women who a combined HRT with estrogen and progestogen or an HRT only with estrogen receive; this risk is dependent on the duration of HRT dependent.

Combined estrogen-progestogen-therapy
In the context of the randomized placebo-controlled study, the Women's Health Initiative Study (WHI-study), und one meta-analysis of prospective epidemiological studies was equally an increased breast cancer risk in

women found, who a combination of estrogen and Progestogen as HRT take; this risk occurs after approx. 3 (1-4) years in appearance (see section 4.8).

Estrogenmonotherapy
The WHIstudy showed no increased breast cancer risk in hysterectomized women under an estrogen monotherapy. Observational studies have mostly a slightly increased risk for a breast cancer diagnosis shown, the however lower was than the risk in users of estrogen-progestogen-combinations (see
section 4.8).

The results a large meta-analysis have shown, that after end of treatment the increased risk over time decreases and the time until return to baseline level age-appropriate baseline risk of the duration of the previous application of the HRT dependent is. If the HRT more than 5 years long used was, can the Risk over a period of 10 years or longer persist.

Hormone replacement therapy (HRT), especially a combined treatment with estrogens and progestogens, leads to an increased breast density in the mammography, which can adversely affect the radiological breast cancer diagnosis impact can.

Ovarian carcinoma
The ovarian carcinoma is very less common than breast cancer. Epidemiological findings of a large meta-analysis suggest a slightly increased risk in women who ,, the in Framework of HRT estrogen-monotherapy or combined estrogen-progestogen-medication apply, which is within 5 years of use shows and after termination the Treatment in Course over time decreases. Some further Studies including the WHI-Study suggest that tothat the corresponding corresponding Risk under the application of a combined HRT comparable or slightly lower is (see section 4.8).

Venous thromboembolism
An HRT is with a 1.3 to 3 times increased risk for venous thromboembolism (VTE) associated, especially for deep vein thrombosis or pulmonary embolism Pulmonary embolisms. the first year of HRT is the occurrence of VTE more likely than later (see section 4.8).

Patients with known thrombophilia have an increased VTE-risk. HRT can increase risk and is therefore in these patients contraindicated contraindicated seesection Section 4.3).

To the generally recognized VTErisk factors include the use of estrogens, an higher age, major surgery, prolonged immobilization, significant obesity (BMI >30 kg/m2), pregnancy/postpartum period, systemic lupus erythematosus (SLE) and cancer. There is no consensus on the possible role of varicose veins in VTE.

How in all postoperative patients must preventive measures to prevent a VTE after the operation considered be. In prolonged Immobilization after a planned operation is recommendedto discontinue HRT 4 to 6 weeks before the procedure to suspend. The treatment should only then be resumed are, when the woman again fully mobilized is.

In women without VTE in the history, but with relatives first degree who already in young years developed VTE suffered, a thrombophilia -screening can beconsidered . Beforehand should. patient be thoroughly informed about the over the limited significance of this procedure advised are (it is only a part of the defects identified, which lead to Thrombophilia thrombophilia). Is a thrombophilic defect detected and are also thromboses in relatives known or is the detected defect severe (e.g. antithrombin, protein S and/or Protein- C-deficiency or a combination of defects), so is a HRT contraindicated.
In patients under a permanent treatment with Anticoagulants should before the application of HRT the benefit-risk ratio carefully weighed be.

If a VTE after start of HRT develops develop, must the medication be discontinued .The patients should be informed ,that they immediately contact a doctor must Doctor record must, if you possible symptoms of a thromboembolism notice (especially painful swelling of a leg, sudden pain in the chest, Shortness of breath).

Coronary heart disease
There are no indications from randomized, controlled studies, that a combined HRT with estrogen and Progestogen or a Estrogen-Monotherapy Women before a myocardial infarction protects, regardless of, whether in them a coronary heart disease is present or not.

Combined Estrogen-Progestogen-Therapy:
The relative risk of coronary heart disease is under a combined HRT with Estrogen and progestogen slightly increased. Since the baseline risk for a coronary heart disease in high degree age-dependent is, is the number the additionally occurring cases, which are due to the HRT from estrogen and progestogen return, in premenopausal healthy women very low. The number increases however with increasing age.

Estrogenmonotherapy:
In randomized controlled trials no evidence for an increased risk of coronary heart disease Heart disease in hysterectomized women under an estrogen-monotherapy found.

Stroke

The combined treatment with estrogen and progestogen and the estrogen-monotherapy are associated with a to up to 1.5-fold increased risk of stroke associated. The relative risk is independent of age and the time span, which since menopause has passed is. As however the basic risk, to suffer a stroke to experience, in a high degree age-dependent is, increases the overall risk of a stroke for Women under a HRT with increasing age to (see section 4.8).

Severe anaphylactic/anaphylactoid reactions
Post marketing have been Cases of anaphylactic/anaphylactoid reactions reported, which developed at some point during the course of estradiol treatment and required emergency medical care.

Patients, who after a treatment with Estradiol an angioedema develop, should ESTRAMON UNO not receive again.

Other disease conditions

- Estrogens can cause fluid retention ;therefore patients with cardiac or renal dysfunction must be carefully monitored ..
- with with pre-existing hypertriglyceridemia must during a Estrogen- or hormone replacement therapy closely monitored be, because in connection with an estrogen therapy under such Circumstances of rare cases of severe increase in triglycerides in plasma with the consequence of pancreatitis reported was.
- Exogenous estrogens can Symptoms of hereditary or acquired angioedema trigger or worsen.
- Estrogens increase the concentration of thyroxine-binding globulin (TBG), thereby it leads to a increase of the total circulating thyroid hormone occurs, which by means of the protein-bound iodine (PBI), the T4 level (column- or radioimmunoassay) or T3 levels (radioimmunoassay) measured is. The T3- resin uptake is reduced, which reflects a TBG-increase reflects. The free T4 and T3 concentrations do not change .. Other Binding proteins can in Serum elevated be, as the corticosteroid-binding globulin (CBG) and the sex-hormone-binding globulin (sex-hormone-binding globulin/SHBG), which leads to an increase of the circulating corticosteroids or. Sex hormones leads. Free or biologically active hormone concentrations remain unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).
- Under a HRT improve the cognitive abilities do not . Thereis evidence of an increased risk for a probable dementia Dementia in women who at the start of continuous combined HRT or an estrogen monotherapy older than 65 years were.

Hepatitis C
In clinical Studies with the combination regimen Ombitasvir/Paritaprevir/Ritonavir with or without Dasabuvir against the hepatitis C virus (HCV), occurred an increase of ALT by more than the 5-fold of the upper limit (Upper Limit of Normal, ULN) significantly more frequently in women who ethinylestradiol-containing medications such as e.g. CHC used. Additionally were during treatment with glecaprevir/Pibrentasvir Increases of ALT in users of ethinylestradiol-containing medications observed. In women who medications with other estrogens than ethinylestradiol used, such as for example Estradiol, was the rate elevated ALT-levels similar to

those whoreceived no estrogens ; due tothe limited number of women who these to women who this others estrogens applied, is nevertheless

caution with the concurrent administration with the combination regimen ombitasvir/paritaprevir/ritonavir with or without Dasabuvir and also with the regimen Glecaprevir/Pibrentasvir indicated. (See section 4.5).

It is known, that a contact sensitization in all topical applications occur can. Although it extremely rarely happens, should women who a contact sensitization to one of the Components of ESTRAMON UNO develop, warned against ,that a severe hypersensitivity reaction may occur , ifthey continue to expose further to the causing substance expose.

The therapy with ESTRAMON UNO is not contraceptive.

Use in children
ESTRAMON UNO must not in children applied become.

4.5 Interactions with other medicines and other interactions

The metabolism of the estrogens (and progestogens) can by the simultaneous use of substances enhanced become, which drug-metabolizing enzymes, especially the cytochrome P450 enzymes, induce . Amongthese substances are anticonvulsants Anticonvulsants such ashow e.g. Phenobarbital, Phenytoin, Carbamazepine) and anti-infectives (such as e.g. Rifampicin, Rifabutin, Nevirapine and Efavirenz).

Ritonavir and Nelfinavir have, when they are used simultaneously with steroid hormones applied, enzyme-inducing properties, although they actually as strong enzyme inhibitors known are.

Herbal medicines, which St. John's Wort (Hypericum perforatum) contain, can the metabolism of estrogens (and progestogens) induce.

Estradiol is predominantly by CYP3A4 metabolized, therefore the simultaneous use of CYP3A4 inhibitors, such as for example ketoconazole and erythromycin, can lead to an increase inestradiol exposure can.

. Effect HRT with estrogens on other medications
It has been shown, that with simultaneous administration estrogen-containing hormonal contraceptives the plasma concentrations of Lamotrigine due to the induction of the lamotrigine glucuronidation significantly reduce. This can the control of seizures impair. Although the possible Interaction between a hormone replacement therapy and lamotrigine not studied was, is assumed ,that a similar interaction in women who Women who both medicines together take, there is, the to a reduction of seizure control lead can.

Pharmacodynamic interactions
In clinical studies with the combination regimen Ombitasvir/Paritaprevir/Ritonavir with or without Dasabuvir against the hepatitis C virus, occurred an increase in ALT by more than 5 times the upper Norm (Upper Limit of Normal, ULN) significant more frequently in women who

ethinylestradiol-containing medications such as e.g. COCs used. In women who medications with other estrogens than ethinylestradiol used, how such as Estradiol, the rate elevated ALT-levels similar to those whodid not receive any estrogens; due to the limited number to women who these other estrogens used, is nevertheless caution with the concurrent administration with the combination regimen Ombitasvir/Paritaprevir/Ritonavir with or without Dasabuvir and also with the regimen Glecaprevir/Pibrentasvir (see section 4.4) required.

In the transdermal application is the first-passeffect in the liver bypassed, so that transdermally applied estrogens (and progestogens) possibly less potent than orally administered hormones through enzyme inducers impaired be.
Clinically can a increased estrogen and progestogen metabolism to a reduced effect of these hormones and to changes of the uterine bleeding pattern lead.

Through an estrogen therapy some laboratory tests can be affected ,such as e.g. glucose tolerance Glucose tolerance- thyroid function tests Thyroid function tests.

## 4.6 Fertility, pregnancy and lactation

Pregnancy
ESTRAMON UNO is not indicated during pregnancy. If it occurs during treatment with ESTRAMON UNO to pregnancy occurs, should the treatment immediately discontinued be.
The most currently available epidemiological studies, which regarding a unintended estrogen exposure of the fetus relevant are, show no teratogenic or fetotoxic effects.

Lactation
ESTRAMON UNO is during lactation not indicated.

## 4.7 Effects on the ability to drive and the ability to operate machinery machines

ESTRAMON UNO has no or a negligible influence on the ability to drive Fitness to drive or the ability to operate of machines.

## 4.8 Side effects

A mild erythema at the application site was the most common reported side effect (16.6%). The erythema was after removal of the patch from the skin at the application site observed. A mild pruritus and a mild skin rash around the application site were also reported.

The side effects are according to frequencies arranged, the most common first. In doing so is the following convention used:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Occasionally (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (Frequency based on the available Data not estimable)

Within each frequency group are the side effects by severity descending listed.

The side effects in the following table were in clinical trials and from the experience after market introduction under ESTRAMON UNO or generally under an estrogentherapy reported.

| **Organ classes** | **Very frequent (≥1/10)** | **Frequent (≥1/100 to <1/10)** | **Occasionally (≥1/1,000 to <1/100)** | **Rare (≥1/10,000 to <1/1,000)** | **Very rare (<1/10,000)** | **Not known* (Frequency based on available Daten nicht abschätzbar)** |
|---|---|---|---|---|---|---|
| **Benign, malignant and non-specific Neuplasms** | | | | | | Breast cancer |
| **Diseases of the Immune system** | | | | Hypersensitivity | Urticaria, anaphylactic Reactions | anaphylactoid reactions |
| **Metabolic and nutritional disorders** | | | | | reduced carbohydrat-Tolerance, Deterioration of porphyria | |
| **Psychiatric disorders** | | Depression, Nervousness, Affect lability lability | Anxiety states | Disorders of Libido | | |
| **Diseases of the nervous system** | Headaches | Insomnia, dizziness | Migraine, dizziness | Paresthesia | Chorea | |

| **Organ classes** | **Very frequent (≥1/10)** | **Frequent (≥1/100 to <1/10)** | **Occasionally (≥1/1,000 to <1/100)** | **Rare (≥1/10,000 to <1/1,000)** | **Very rare (<1/10,000)** | **Not known* (Frequency based on available data not estimable)** |
|---|---|---|---|---|---|---|

| | | | | | | |
|---|---|---|---|---|---|---|
| **Eye disorders** | | | Visual disturbances, dry eyes | | Contact lens intolerance | |
| **Vascular disorders** | | | Hypertension, Palpitation | venous thrombo-embolism | | Embolism |
| **Diseases of Gastrointestinal tract** | | Nausea, dyspepsia, diarrhea, abdominal pain, bloating, feeling of fullness, increased appetite | vomiting | | | |
| **Liver- and bile-duct diseases gene** | | | | Cholelithiasis, alteration of liver function and bile flow | | |
| **Diseases of the skin and subcutaneous tissue** | Reactions at the application site**, Erythema | Acne, skin rash, dry skin, pruritus | Skin discoloration | Alopecia | Skin necrosis, hirsutism | Angioedema, contact dermatitis, chloasma |
| **Musculoskeletal system, connective tissue and bone disorders gen** | | Back pain-zen | Joint pain-zen, muscle-cramps | Myasthenia | | Pain in the extremities |
| **Diseases of the reproductive organs and the mammary gland** | Breast tension, breast pain, dysmenorrhea, menstrual complaints | Breast enlargement, menorrhagia, discharge, ir- regular va- vaginal bleeding, uterine cramps, | | uterine leiomyoma, fallopian tube cysts, cervical polyps, secretion from the mammary gland | | fibrocystic mastopathy |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | vaginal infections, endometrial hyperplasia | | | | |
| **General disorders and complaints at the application site** | | pain, asthenia, peripheral edema, weight fluctuations | | allergic reactions, loss of appetite sigkeit | Nosebleeds | |
| **Examinations** | | | increased Transa-minases | | | abnormal Liver-function tests |

* After market introduction reported
** Reactions at the application site including local bleeding, Bruise, Burning, Skin disorders, Dry skin, Eczema, Edema, Skin redness, Inflammation, Skin irritation, Pain, Papules, Sensitivity disorder, Itching, Skin rash, Skin discoloration, Skin pigmentation, Swelling, Urticaria and Blisters.

Breast cancer
In women who a combined Estrogen-Progestogen-therapy over more than 5 years conducted had, was the risk for a breast cancer diagnosis up to 2-fold increased.
In users of estrogenmonotherapy is the increase of risk lower than in users of estrogenprogestogen-combination preparations.
The level of the risk is dependent on the duration of use (see section 4.4).

It are estimates of the absolute risk based on the Results of the largest randomized, placebo-controlled study (WHI-study) and the largest meta-analysis of prospective epidemiological studies presented represented.

So far largest meta-analysis of prospective epidemiological studies

Estimated additional breast cancer risk after 5-year use in women with a BMI of 27 (kg/m²)

| **Age at start of HRT (years)** | **Incidence per 1,000 non-users of HRT over 5 years (50-54 years)*** | **Relative risk** | **Additional cases in 1,000 HRT users after 5 years Estrogen monotherapy** |
|---|---|---|---|
| **Estrogen monotherapy** | | | |
| 50 | 1.2 | 2.7 | 2.7 |
| **Estrogen-progestogen combination therapy** | | | |
| 50 | 13.3 | 1.6 | 8.0 |

* based on the baselineincidence rates in England in year 2015 among women with a BMI of 27 (kg/m2).
Note: As itself the background incidence of breast cancer from EU country to EU country differs, changes itself also the number of additional breast cancer cases proportionally.

Estimated additional breast cancer risk after 10-year use in women with a BMI of 27 (kg/m²)

| **Age at start of HRT (years)** | **Incidence per 1,000 non-users of HRT over a period of 10 years (50-59 years)*** | **Relative risk** | **Additional cases per 1,000 HRT users after 10 years** |
|---|---|---|---|
| **Estrogen monotherapy** | | | |
| 50 | 26.6 | 1.3 | 7.1 |
| **Estrogen-progestogen combination therapy** | | | |
| 50 | 26.6 | 1.8 | 20.8 |

*based on the baseline incidence rates in England in year 2015 in women with a BMI of 27 (kg/m2)
Note: As the background incidence of breast cancer from EU country to EU country varies distinguisheschanges in yourself also the number of additional breast cancer cases proportional.

WHI-studies in the USA – additional breast cancer risk after 5-year HRT

| **Age group (years)** | **Incidence per 1,000 women in the placebo arm over a time period of 5 years** | **Relative risk (95 % CI)** | **Additional cases in 1,000 HRT users over a period of 5 years (95% CI)** |
|---|---|---|---|
| **Estrogen monotherapy (CEE)** | | | |
| 50-79 | 21 | 0.8 (0.7-1,0) | -4 (-6-0)* |
| **Estrogen and progestin (CEE+MPA)#** | | | |
| 50-79 | 17 | 1.2 (1.0-1.5) | +4 (0-9) |

* In restriction of Evaluation on women who before the study did not HRT use had, appeared the risk during the first 5 years of treatment not increased: After 5 years, the risk was higher than in untreated women.
* WHI-study in women without uterus, which did not show increased breast cancer risk showed

Endometrial carcinoma
Postmenopausal Women with intact Uterus
Approximately 5 out of 1,000 women with intact Uterus, who do not HRT use, develop an Endometrial carcinoma. In women with intact Uterus is the use of estrogenmonotherapy not recommended, as this the risk of endometrial carcinoma increases (see section 4.4).
In Dependence on the duration of estrogenmonotherapy and the estrogen dose the increased risk of endometrial carcinoma in epidemiological studies at 5 to 55 additional diagnosed cases per 1,000 women in age between 50 and 65 years.

By adding a progestogen to estrogenmonotherapy for at least 12 days per cycle can this increased risk avoided be. In the Million Women Study, after 5-year use of a combined HRT

(sequential or continuous) the risk of an endometrial carcinoma not increased (RR 1.0 [95% CI 0.8-1.2]).

Ovarian carcinoma
Application of estrogen-monopreparations or of estrogen-progestogen-combination preparations for HRT is associated with minor slightly increased risk, that a ovarian carcinoma diagnosed is (see section 4.4).

From a meta-analysis of 52 epidemiological studies shows an increased risk of ovarian carcinoma for Women highlight, who currently HRT use, in comparison to women who HRT never used have (RR 1.43, 95% CI 1.31-1.56). In women in age between 50 and 54 years, who a HRT 5 years long apply, occurs one additional case per
2,000 users occur. In women at age between 50 and 54 years, who do not HRT use, are over a 5-year period approximately 2 cases of ovarian carcinoma per 2,000 women diagnosed.

Venous thromboembolisms
The risk of the occurrence of a venous Thromboembolism (VTE), e.g. a thrombosis of the deep leg- or. or a pulmonary embolism Pulmonary embolismis with a HRT increased by 1.3 to 3 times increased . The. The Occurrence of such an event is during the first year of treatment more likely than in the subsequent years of the treatment (see section 4.4). The relevant Results of the WHI-studies are in the following presented.

WHI-studies – additional risk for VTE after 5-year HRT

| **Age group (years)** | **Incidence per 1,000 women in the Placebo arm over a period of 5 years** | **Relative risk (95% CI)** | **Additional cases per 1,000 HRT users after 5 years** |
|---|---|---|---|
| **Oral estrogenmonotherapy*** | | | |
| 50-59 | 7 | 1.2 (0.6-2,4) | 1 (-3-10) |
| **Combined oral estrogen-progestogentherapy** | | | |
| 50-59 | 4 | 2.3 (1.2-4.3) | 5 (1-13) |

* Study in women without Uterus

Coronary Heart disease
In Users a combined Estrogen-Progestogen-HRT at age of over 60 years is the Risk for the Development one coronary heart disease slightly increased (see section 4.4).

Stroke
The use of estrogenmonotherapy or a combined estrogenprogestogen-Therapy is associated with a to up to 1.5-fold increased risk for an ischemic stroke. The risk for a hemorrhagic Stroke is under a HRT not increased.

This relative risk is independent of age or of the duration of use. Since the baseline risk however strong from age depends, increases the overall risk in women under a HRT with increasing age (see section 4.4).

Combined WHI-Studies – additional risk for ischemic stroke* after 5-year HRT

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

* It was not between ischemic and hemorrhagic stroke distinguished.

Soybean oil (Ph.Eur.) can cause allergic reactions.

In connection with a Estrogen-/Progestogen treatment were further undesirable adverse drug reactions reported

- Diseases of the gallbladder
- Skin- and subcutaneous disorders: Chloasma, erythema multiforme, erythema nodosum, vascular purpura
- probable dementia in women in age of over 65 years (see section 4.4)
- Jaundice
- Breast adenoma

Reporting of suspected of adverse reactions
The reporting of suspected of adverse reactions after the approval is of great importance. It enables a continuous monitoring of the benefit-risk ratio of the medicinal product. Healthcare professionals Health professions are requested, any suspected case of an adverse reaction to the

Federal Institute for Drugs and Medical Devices Dept. Pharmacovigilance
Kurt-Georg-Kiesinger-Allee 3 D-53175 Bonn
Website: www.bfarm.de

to report.

4.9 Overdose

A acute overdose is unlikely due to the method of application unlikely. The most common symptoms of overdose in clinical use are breast tension Breast tension and/or Vaginal bleeding. If such symptoms occur, a dose reduction should be considered . By. the Remove of the Patches can the overdose effects quickly be resolved.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Estrogens
ATC code: G03C A03

The active ingredient, synthetic 17-β-Estradiol, is chemically and biologically identical to the endogenous human estradiol identical, substitutes the loss of estrogen production in menopausal Women and reduces the associated symptoms Complaints.

prevent the loss of bone mass after menopause or after an oophorectomy Ovariectomy before.

Information on the clinical studies
Relief of caused by the estrogen deficiency caused symptoms and Influence the bleeding A relief of Menopausal symptoms was in the first weeks of the treatment achieved.

Osteoporosis prevention
Estrogen deficiency in menopause is associated with an increased bone turnover and a loss an Bone mass accompanied.
The effect of estrogens on the bone density is dose-dependent. The protection is apparently as long effective, as the Treatment continued is. After termination of HRT is the loss of bone mass with the untreated women comparable.
From the WHI-study and meta-analyses of further studies shows that, that the current use of an HRT, alone or in combination with a progestogen, in predominantly healthy women the risk of hip-, vertebral- or other osteoporotic fractures reduces. An HRT could also fractures in women with low bone density and/or proven osteoporosis prevent, for this there are however only limited findings available.

5.2 Pharmacokinetic properties

Absorption
Through the transdermal application of estradiol are with lower total doses than with the oral application therapeutic Plasma concentrations reached, whereby in the transdermal application also the plasma levels of estrone and estrone conjugates are lower ..

ESTRAMON UNO 50/- UNO 100
ESTRAMON UNO 50/- UNO 100
During the continuous application of ESTRAMON UNO 50 or. - UNO 100 a mean plasma concentration (Cav) of approx. 31.43 pg /mlor . 70.97pg /mlwas achieved . Themaximum maximum Plasma concentration (Cmax) was in the range of 56.1 pg/ml or. 116.5 pg/ml. After removal of the patch returns the Estradiol plasma levels within 12–24 h return to the baseline values back.

ESTRAMON UNO 75
In the continuous use of ESTRAMON UNO 75 was an average plasma concentration (Cav) of approx. 55.7 pg/ml reached, which at the end of a dosing interval of seven days still 32.3 pg/ml amounted to . After removal of the patch returns the estradiol plasma level within from 12-24 h again to the baseline values back.

Distribution
Estradiol is to more than 50% bound to plasma proteins such as the sex hormone-binding globulin and albumin bound. Only 2% are free and biologically active.

Biotransformation
Transdermally applied estradiol is via the same pathway metabolized as the endogenous hormone. Estradiol is primarily in the liver to estrone metabolized, and then to estriol, epi-estriol and catechol-estrogens, which then to sulfates and glucuronides conjugated are. The cytochrome P450 isoforms CYP1A2 and CYP3A4 catalyze the hydroxylation of estradiol forming

estriol. Estriol is in humans by UGT1A1 and UGT2B7 glucuronidated. The estradiol metabolites are also via the enterohepatic circulation metabolized.

Elimination
The sulfates and glucuronide-esters are together with a small portion of Estradiol and various other metabolites in the urine excreted. Only a small amount is excreted with the feces excreted. Since Estradiol a short half-life has (approximately 1 hour), decrease within 24 hours after removal of the patch the serum concentrations of estradiol and Estrone again to the baseline values back.

5.3 Preclinical data on safety

The toxicity profile of estradiol is well known.
The continuous use of natural and synthetic estrogens over a long period increases in certain animal species the incidence of tumors in Breast, uterus, cervix, vagina, testes and liver as well as the frequency of tumors of the lymphatic system and the pituitary gland.

6. PHARMACEUTICAL INFORMATION

6.1 List of the other components

- Matrix: Poly[(2-ethylhexyl)acrylate-co-methylacrylate-co-acrylic acid-co-(2,3-epoxypropyl)methacrylate] (62.2:32.0:5.7:0.03), RRR-alpha-Tocopherol-preparation (USP) (contains soybean oil [Ph.Eur.])
- Backing film: polyethylene terephthalate
- Release liner: polyethylene terephthalate, siliconized

6.2 Incompatibilities

Not applicable.

6.3 Duration of Shelf life

2 years

6.4 Special precautions for the storage

Do not store above 30 °C.

6.5 Type and content of Container

Each ESTRAMON UNO-patch is individually in an aluminum pouch packaged.

Packages with 4, 12 and 16 transdermal patches
It may not be all pack sizes in the market placed.

6.6 Special precautions for the disposal and other instructions for handling

Disposal

After use Use is the ESTRAMON UNO-patch to fold (adhesive surface inward !) andwith the household waste to dispose ..

medicinal product or waste material or Waste material is according the national requirements to dispose.

7. MARKETING AUTHORIZATION HOLDER

Hexal AG Industriestraße 25
83607 Holzkirchen
Phone: (08024) 908-0
Fax: (08024) 908-1290
Email: medwiss@hexal.com

8. APPROVAL NUMBERS

ESTRAMON UNO 50
36415.00.00

ESTRAMON UNO 75
40778.00.00

ESTRAMON UNO 100
36415.01.00

9. DATE OF GRANTING OF APPROVALS/EXTENSION OF APPROVALS ESTRAMON UNO 50/- 100

Date of granting of approvals:
9. June 1997
Date of last extension of Approvals:
9. June 2002

ESTRAMON UNO 75
Date of granting of approval:
18. January 2002
Date of last renewal of approval:
1. April 2008

10. STATUS OF INFORMATION

September 2023

11. SALES RESTRICTION

Prescription only