

NEW ZEALAND DATA SHEET

ESTRADERM TTS[®]

Estradiol (as hemihydrate)

25, 50 and 100mcg/24hrs Transdermal Patches

Qualitative and quantitative composition

Estradiol (as hemihydrate).

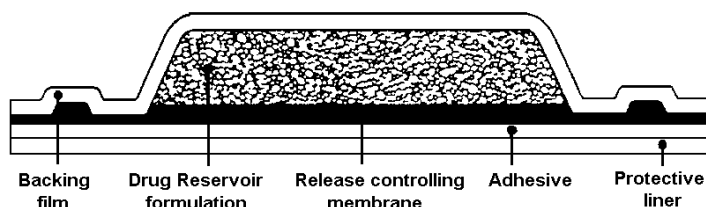
Systems with 2, 4 and 8 mg active substance are available.

Pharmaceutical form

Pharmaceutical form

Estraderm TTS[®] is a thin, multilayer, transparent transdermal patch for application to an area of intact skin. The drug reservoir is sealed between a backing film and a release-controlling membrane which limits the rate at which estradiol is continuously released across the adhesive layer to the skin. The active substance of the patch penetrates the skin and passes directly into the bloodstream.

Cross section:



Dosage strength

The following three systems are available:

| | Estraderm TTS 25 | Estraderm TTS 50 | Estraderm TTS 100 |
|-----------------------------------|-------------------------|-------------------------|--------------------------|
| Nominal rate of Estradiol release | 25 micrograms/day | 50 micrograms/day | 100 micrograms/day |
| Content of Estradiol | 2 mg | 4 mg | 8 mg |
| Drug-releasing area | 5 cm ² | 10 cm ² | 20 cm ² |
| Imprint (backing side) | CG DWD | CG EFE | CG FBF |

Release of the active substance is maintained for 4 days.

Clinical particulars

Therapeutic indications

- Treatment of signs and symptoms of estrogen deficiency due to the menopause, whether natural or surgically induced, e.g. hot flushes, sleep disturbances, and urogenital atrophy, as well as accompanying mood changes.
- Prevention of accelerated postmenopausal bone loss (see Dosage and method of administration and Special warnings and special precautions for use).

In women with an intact uterus, estrogens should always be supplemented by sequential administration of a progestogen.

Dosage and method of administration

Adults and elderly

Dosage

For all therapeutic indications, the lowest effective dose should be used.

Hormone replacement therapy (HRT) involving either estrogen alone or estrogen-progestogen combined therapy should only be continued as long as the benefits outweigh the risks for the individual.

Estraderm TTS should be applied twice weekly, e.g. the system should be changed once every 3 to 4 days. Treatment should be initiated with the lowest dose. If the dose selected fails to eliminate the signs and symptoms of estrogen deficiency, a higher dose should be given.

Breast discomfort, breakthrough bleeding, fluid retention or bloating (if persisting for more than 6 weeks) are generally signs that the dose is too high and needs to be lowered.

Epidemiological data suggest that estrogen therapy given for at least 5 years early in the menopause reduces subsequent hip and Colles' fractures by about 50%, and vertebral fractures by up to 90%.

Therapeutic regimen

Estraderm TTS is administered as continuous treatment (uninterrupted application twice weekly). In women with an intact uterus, estrogen therapy should be supplemented by sequential administration of a progestogen (e.g. medroxyprogesterone acetate 10 mg, norethisterone 5 mg, norethisterone acetate 1-5 mg, or dydrogesterone 20 mg per day) to be taken at least on the last 12 days of each 4-week treatment cycle. Withdrawal bleeding usually occurs following the 12 days or more of progestogen administration.

Administration

Immediately after removal of the protective liner (see figure below), the patch should be applied to an area of clean, dry, and intact skin.



The site selected should be one at which little wrinkling of the skin occurs during movement of the body, e.g. buttock, hip, or abdomen, and which is not exposed to sunlight, e.g. those areas normally covered by clothing.

Experience to date has shown that less irritation of the skin occurs on the buttock than at other sites of application. It is therefore recommended to apply the patch to the buttock.

The area of skin should be non-greasy and free of irritation.

Estraderm TTS must not be applied to the breast. The system should not be affixed twice in succession to the same skin site.

If a woman has forgotten to apply a patch, she should apply a new patch as soon as possible.

The subsequent patch should be applied according to the original treatment schedule. The interruption of treatment might increase the likelihood of recurrence of symptoms.

Children

Estraderm TTS should not be used in children.

Contraindications

Estraderm TTS should not be used by women with any of the following conditions:

- Known, past or suspected cancer of the breast,
- Known or suspected cancer of the endometrium or other estrogen-dependent neoplasia,
- Undiagnosed abnormal vaginal bleeding,
- Severe hepatic disease,
- History of or current venous thromboembolism (VTE) (e.g. deep vein thrombosis, pulmonary embolism),

- Known thrombophilic disorders or thrombophlebitis,
- History of or current arterial thromboembolic disease (e.g. coronary heart disease, stroke),
- Porphyria,
- Known hypersensitivity to estrogens or any other components of Estraderm TTS,
- Known or suspected pregnancy,
- Breastfeeding.

Special warnings and special precautions for use

Warnings

For all therapeutic indications, the lowest effective dose should be used and consideration should be given to the shortest duration of use. Treatment should only be continued as long as the benefits outweigh the risks for the Individual.

The Medicines Adverse Reactions Committee advises that combined HRT should not be used for longer than 3 – 4 years.

Osteoporosis

When initiating HRT for the prevention of osteoporosis, careful consideration should be given to the benefits versus the risks for the individual. Potential alternative therapies should be considered if the risks outweigh the benefits. Periodic re-evaluation for continuing treatment is recommended.

Contact sensitisation

Contact sensitisation is known to occur with all topical applications. Although it is extremely rare, women who develop contact sensitisation to any of the components of the patch should be warned that a severe hypersensitivity reaction may occur with continuing exposure to the causative agent.

Severe anaphylactic/anaphylactoid reactions and Angioedema

Cases of anaphylactic/anaphylactoid reactions, which developed anytime during the course of Estraderm TTS treatment and required emergency medical management, have been reported in the post marketing setting. Involvement of skin (hives, pruritis, swollen lips-tongue-face) and either respiratory tract (respiratory compromise) or gastrointestinal tract (abdominal pain, vomiting) has been noted. Angioedema involving the eye/eyelid, face, larynx, pharynx, tongue and extremity (hands, legs, ankles and fingers) with or without urticaria requiring medical intervention has occurred in the post marketing experience of using Estraderm TTS. If angioedema involves the tongue, glottis, or larynx, airway obstruction may occur. Patients who develop angioedema after treatment with Estraderm TTS should not receive Estraderm TTS again .

Cardiovascular disease

HRT should not be used to prevent cardiovascular disease

Large clinical trials (Women's Health Initiative and Heart and Estrogen/Progestin Replacement study) showed an increased risk of cardiovascular events with the combined HRT products used in these studies. The risk for estrogen-only HRT products is still under evaluation.

The Women's Health Initiative (WHI) is a randomised clinical trial conducted with continuous combined oral conjugated equine estrogens (CEE) and medroxyprogesterone acetate (MPA) for an average follow-up of 5.2 years. In the WHI trial, the absolute excess risk of coronary heart disease was 7 additional cases per 10,000 person-years (37 versus 30) in HRT-treated women and the relative risk was 1.29.

In addition, the WHI study showed an increased incidence of stroke. The absolute excess risk was 8 additional cases per 10,000 person-years (29 versus 21) in HRT-treated women and the relative risk was 1.41.

The Heart and Estrogen/Progestin Replacement Study (HERS), which is a controlled clinical trial of secondary prevention in postmenopausal women with documented heart disease conducted with CEE and MPA, showed an increased risk of cardiovascular events in the first year of use and no cardiovascular benefit thereafter.

For transdermal estrogen-only and estrogen-progestogen combined HRT products, there are no randomised controlled trials to date assessing the HRT-associated risk of cardiovascular morbidity or mortality, or stroke. Therefore there are no data to support the conclusion that the frequency of cardiovascular events and stroke is different with Estraderm TTS.

Venous thromboembolism

Estrogen-only and estrogen-progestogen combined HRT are associated with a higher risk of developing venous thromboembolism (VTE), e.g. deep vein thrombosis or pulmonary embolism.

Two randomised controlled trials (WHI and HERS) and epidemiological studies have found a two- to threefold higher risk for users compared with non-users.

The WHI study (see subsection Cardiovascular disease) showed an increased incidence of pulmonary embolism. The absolute excess risk was 8 additional cases per 10,000 person-years (15 versus 7) in HRT-treated women and the relative risk was 2.13.

The increase in risk was found only in current users and did not persist in former users. The risk appeared to be higher in the first years of use compared to later years.

For non-users, it is estimated that the number of cases of VTE that would occur over a 5-year period is about 3 per 1000 women aged 50-59 years and 8 per 1000 women aged 60-69 years. It is estimated that in healthy women who use HRT for 5 years, the number of additional cases of VTE would be between 2 and 6 per 1000 women aged 50-59 years and between 5 and 15 per 1000 women aged 60-69 years.

Risk/benefit should therefore be carefully weighed in consultation with the individual when prescribing HRT to women with a risk factor for the occurrence of VTE that is not already mentioned under Contraindications.

Generally recognised risk factors for VTE include a personal history or family history (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic predisposition) of thromboembolic disease, severe obesity (Body Mass Index $> 30 \text{ kg/m}^2$) and systemic lupus erythematosus (SLE). The risk of VTE also increases with age. There is no consensus about the possible role of varicose veins in VTE.

A history of recurrent spontaneous abortions should be investigated to exclude thrombophilic predisposition. In women in whom this diagnosis is confirmed, the use of HRT is viewed as contraindicated.

The risk of VTE may be temporarily increased with prolonged immobilisation, major elective or posttraumatic surgery, or major trauma. In women on HRT, scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Depending on the nature of the event and the duration of the immobilisation, consideration should be given to temporarily stopping HRT several weeks earlier, if possible. The treatment should not be restarted until the woman is completely mobile.

Women should be told to contact their doctor immediately if they become aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea). If venous thromboembolism develops after initiating therapy, the drug should be discontinued.

Breast cancer

Randomised controlled trials and epidemiological studies have reported an increased risk of breast cancer in women taking HRT. Women using estrogen-progestogen combined HRT had

a possibly higher risk as compared with women who used unopposed estrogens. The excess risk of breast cancer increases with the duration of intake of estrogen-only and estrogen-progestogen combined HRT.

There is evidence arising from the WHI study (see subsection Cardiovascular disease) which shows an absolute excess risk of invasive breast cancer of 8 additional cases per 10,000 person-years (38 versus 30) in the HRT-treated women and a relative risk of 1.26.

A meta-analysis reanalysed 51 epidemiological studies conducted between the 1970s and the early 1990s. The cumulative incidence of breast cancer between the ages of 50 and 70 in non-users of HRT is about 45 per 1000 women. The cumulative excess numbers of breast cancers diagnosed between these ages per 1000 women who began use of HRT at age 50 to 70 and used it for 5, 10, and 15 years, are estimated to be 2, 6, and 12, respectively.

The number of additional cases of breast cancer is broadly similar for women who start HRT regardless of age at start of treatment (between ages of 45 and 65).

The excess risk seems to return to baseline in the course of about five years after stopping treatment.

For transdermal estrogen-only and estrogen-progestogen combined HRT products, no large randomised clinical trials to date have assessed the HRT-associated risk of breast cancer.

Therefore there are no data to support the conclusion that the frequency of breast cancer is different with Estraderm TTS.

Endometrial cancer

The risk of endometrial cancer in users of unopposed estrogens who have an intact uterus is greater than in non-users and appears to depend on the duration of treatment and the estrogen dose. The greatest risk appears to be associated with prolonged use. It has been shown that adequate concomitant progestogen therapy lowers the incidence of endometrial hyperplasia and therefore the potential risk of endometrial carcinoma associated with prolonged use of estrogen therapy.

Estrogens, regardless of their origin, increase the risk of endometrial cancer. Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding or spotting.

Ovarian cancer

An increased risk of ovarian cancer in menopausal women taking estrogen only replacement therapy was observed in a large US study enrolling over 40,000 women on HRT. These women were followed up for a mean duration of 13.4 years (range 1 month to 19.8 years). The increased risk of ovarian cancer in those taking estrogen replacement therapy was 80%, RR 1.8 (95% CI, 1.1-3.0) at 10 to 19 years. This risk increased with duration of use; RR for 20 years or more years of use was 3.2 (95% CI, 1.7-5.7). This equates to approximately 3 and 8 additional cases per 10,000 women-years at these time points; (the incidence of ovarian cancer in non-users was 4.4 per 10,000 women years). This observation was most obvious in those women on long-term estrogen replacement therapy who had a prior history of hysterectomy (defined as simple hysterectomy or hysterectomy with unilateral oophorectomy). In this subpopulation, the RR was 2.0 (95%CI, 0.96-4.3) for between 10 and 19 years of use and 3.4 (95% CI, 1.6-7.5) for 20 years or more.

Dementia

In a randomized placebo-controlled ancillary study of the WHI, the Women's Health Initiative Memory Study (WHIMS), women aged 65 and older (average age 71) treated with oral CEE and MPA for an average follow-up of 4 years were reported to have a two-fold increase in the risk of developing probable dementia. The absolute excess risk of probable

dementia was 23 additional cases per 10,000 person-years (45 versus 22) in CEE/MPA treated women and the relative risk was 2.05.

In a randomised, placebo-controlled, oestrogen alone ancillary study of the WHI (WHIMS), the absolute excess risk of probable dementia after an average follow-up of 5.2 years was 12 additional cases per 10,000 person-years (37 versus 25) in CEE treated women and the relative risk was 1.49, which did not reach statistical significance ($p = 0.18$) compared to placebo.

Since both substudies were conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women.

The estrogen-only sub-study of the WHIMS is currently on-going and no data are available yet. It is therefore unknown whether these findings apply to estrogen-only therapy.

For transdermal estrogen-only and estrogen-progestogen combined products, no large randomised clinical trials have assessed the HRT-associated risk of probable dementia to date. Therefore there are no data to support the conclusion that the frequency of probable dementia is different with Estraderm TTS.

Angioedema

Oestrogens may induce or exacerbate symptoms of angioedema, in particular in women with hereditary angioedema

Precautions

Before initiating or re-instituting HRT, a complete personal and family medical history, and an appropriate physical (including pelvic and breast) examination should be performed (see Contraindications and Special warnings and special precautions for use). During treatment, periodic check-ups of a nature and frequency adapted to the individual woman are recommended. A careful appraisal of the risks and benefits should be undertaken over time in women treated with HRT and the need for HRT should be re-evaluated periodically.

Women should be advised that changes in their breasts should be reported to their doctor or nurse. Investigations, including mammography, should be carried out in accordance with currently accepted screening practices and adapted to the clinical needs of the individual woman.

Consideration should be given to the lowest dose and the shortest duration of use.

In all cases of undiagnosed persistent or irregular vaginal bleeding, adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out abnormality and the treatment should be re-evaluated.

Hysterectomised women who require postmenopausal hormone therapy should receive estrogen-only replacement therapy unless otherwise indicated (e.g. endometriosis).

If any of the following conditions are present or have occurred previously (including during pregnancy or a previous hormone treatment), the woman should be closely monitored, in particular: leiomyoma (uterine fibroids) or endometriosis, thromboembolic disorders, heart failure, hypertension, renal or hepatic (e.g. liver adenoma) disorders, diabetes mellitus with or without vascular involvement, cholelithiasis, migraine or severe headache, systemic lupus erythematosus, endometrial hyperplasia, epilepsy, asthma, otosclerosis, gallbladder disease, estrogen-related jaundice and pruritus.

It should be taken into account that these conditions may recur or be aggravated during treatment with estrogens.

Caution is advised when risk factors for estrogen-dependent tumours (e.g. first-degree blood relatives who have ever had breast cancer) are present.

If worsening of any of the above mentioned conditions is diagnosed or suspected during HRT, the benefits and risks of HRT should be reassessed on an individual basis.

Therapy should be discontinued in the following situations: jaundice or deterioration of liver function, a significant increase in blood pressure, new onset of migraine-type headache and pregnancy, or if a condition described under Contraindications develops.

Estrogens may cause fluid retention and therefore women with cardiac or renal dysfunction should be carefully monitored.

Women with hypertriglyceridaemia should be followed closely during HRT, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oral estrogen therapy in these women.

Although observations to date suggest that estrogens, including transdermal estradiol, do not impair carbohydrate metabolism, diabetic women should be monitored during initiation of therapy until further information is available.

Unopposed estrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore, the addition of a progestogen to estrogen replacement therapy is recommended in women who have undergone hysterectomy and who are known to have residual endometriosis.

Women should be advised that Estraderm TTS is not a contraceptive, nor will it restore fertility.

Thyroid function should be monitored regularly in patients who require thyroid hormone replacement therapy and who are also taking oestrogen in order to ensure that thyroid hormone levels remain within an acceptable range.

Interactions with other medicinal products and other forms of interaction

The metabolism of estrogens and progestogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepine), meprobamate, phenylbutazone and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz).

Caution should be used if the woman is receiving protease inhibitors (e.g. ritonavir and nelfinavir), which are known as strong inhibitors of cytochrome P450 enzymes, and by contrast exhibit inducing properties when used concomitantly with steroid hormones.

Herbal preparations containing St. John's wort (*Hypericum perforatum*) may induce the metabolism of estrogens and progestogens.

Clinically, increased metabolism of estrogens and progestogens may lead to decreased effects and changes in the uterine bleeding profile.

With transdermal HRT administration, the first-pass effect in the liver is avoided and thus transdermally applied estrogens may be less affected by enzyme inducers than oral hormones.

Some laboratory tests may be influenced by oestrogen therapy, such as tests for glucose tolerance or thyroid function.

Pregnancy and lactation

Estraderm TTS should not be used during pregnancy and lactation. Estrogens may cause foetal harm when administered to a pregnant woman.

Effects on ability to drive and use machines

None known.

Adverse effects

Adverse drug reactions from clinical trials (Table 1) and post-marketing experience are listed according to the system organ class in MedDRA. Within each system organ class, the adverse drug reactions are ranked by frequency, the most frequent first. Within each frequency

grouping, adverse drug reactions are presented in the order of decreasing seriousness. In addition the corresponding frequency using the following convention (CIOMS III) is also provided for each adverse drug reaction: very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$); very rare ($< 1/10,000$), including isolated reports and not known.

Table 1

| | |
|---|--|
| Neoplasms benign, malignant and unspecified (including cysts and polyps) | |
| Uncommon: | Breast cancer. |
| Immune system disorders | |
| Very rare: | Anaphylactoid reaction (5). |
| Not known*: | Hypersensitivity (incl. anaphylactic reaction and angioedema). |
| Psychiatric disorders | |
| Not known*: | Depression, nervousness, affect lability, libido disorder. |
| Nervous system disorders | |
| Common: | Headache. |
| Rare: | Dizziness. |
| Not known*: | Migraine. |
| Cardiac disorders | |
| Very rare: | Embolism , hypertension , varicose veins (including exacerbation). |
| Gastrointestinal disorders | |
| Common: | Nausea, abdominal pain, abdominal distension. |
| Very rare: | Liver function tests abnormal, jaundice cholestatic . |
| Not known*: | Cholelithiasis, vomiting, diarrhoea, gallbladder disorder . |
| Skin and subcutaneous tissue disorders | |
| Very rare: | Contact dermatitis, pigmentation disorders, generalised pruritus, generalised exanthema. |
| Not known*: | Alopecia, chloasma. |
| Musculoskeletal and connective tissue disorders | |
| Rare: | Pain in extremity (leg pain (4)). |
| Not known*: | Back pain. |
| Reproductive system and breast disorders | |
| Very common: | Breast discomfort (1), breakthrough bleeding (2,3). |
| Not known*: | Endometrial hyperplasia, uterine leiomyoma, breast pain, breast tenderness . |
| General disorders and administration site conditions | |
| Very common: | Applicationsite reactions. |
| Rare: | Oedema, weight increased or decreased. |

(*) Reported in post-marketing experience.

(1) Sign of oestrogen effect, sign of overdose.

(2) Usually a sign of oestrogen overdose.

(3) If the oestrogen is adequately combined with a progestogen, regular withdrawal bleeding occurs, as observed in the normal menstrual cycle. Like any oestrogen therapy, transdermal oestrogen treatment can induce endometrial hyperplasia unless oestrogen intake is supplemented by adequate doses of a progestogen .

(4) Not related to thromboembolic disease and usually transient, lasting 3-6 weeks. If symptoms persist, the oestrogen dose should be reduced.

Other adverse reactions have been reported in association with some estrogen-progestogen treatments:

- Estrogen-dependent neoplasms, benign and malignant, e.g. endometrial cancer,

- Venous thromboembolism, e.g. deep leg or pelvic venous thrombosis and pulmonary embolism,
- Stroke,
- Myocardial infarction
- Dementia.
- Dry Eyes
- Tear film composition changes

Overdose

Owing to the mode of administration, overdose of estradiol is unlikely to occur, but can if necessary be rapidly reversed by removing the patch.

Pharmacological properties

Pharmacodynamic properties

Pharmacotherapeutic group: Estrogens (ATC code G03CA03)

Estradiol

Like all steroid hormones, estrogens exert their metabolic effects intracellularly. In the cells of the target organs, estrogens interact with a specific receptor to form a complex which modulates gene transcription and subsequent protein synthesis. Such receptors have been identified in various organs, e.g. hypothalamus, pituitary, vagina, urethra, uterus, breast and liver, and in osteoblasts.

Estradiol, which from the menarche to the menopause is produced mainly by the ovarian follicles, is the most active estrogen. It is largely responsible for the development and maintenance of the female urogenital system and of secondary sexual characteristics. After the menopause, when the ovaries have ceased to function, only small amounts of estradiol are still produced, from aromatisation of androstenedione and to a lesser extent testosterone, by the aromatase enzyme, yielding estrone and estradiol, respectively. Estrone is further transformed to estradiol by the enzyme 17 β -hydroxysteroid-dehydrogenase. Both enzymes occur in fat, liver, and muscle tissue.

In many women, the cessation of ovarian estradiol production results in vasomotor symptoms (hot flushes), sleep disturbances, and progressive atrophy of the urogenital system. These disorders can be largely eliminated by means of estrogen replacement therapy. It has also been shown that HRT or estrogens are effective in preventing the decline in skin thickness seen after the menopause.

It is well established that estrogen replacement therapy prevents postmenopausal bone loss, especially if initiated early in the menopause.

Transdermal therapy with Estraderm TTS delivers the physiological estrogen estradiol in unchanged form directly into the bloodstream. Estradiol concentrations are raised to levels similar to those in the early follicular phase and maintained over the application period of 3-4 days. In the plasma the concentration ratio of estradiol (E2) to estrone (E1) undergoes a corresponding shift from between 1:5 and 1:2 to approx. 1:1, e.g. to values similar to those recorded before the menopause in women with normally functioning ovaries. Estraderm TTS thus provides physiological estrogen replacement.

Following the application of Estraderm TTS for 28 days, no effect has been observed on the concentrations or activity of the blood coagulation factors fibrinopeptide A, high-molecular-weight fibrinogen, and antithrombin III. After this period of 28 days, transdermally administered estradiol did not induce any change in the concentrations either of circulating renin substrate or of the sex-hormone-binding, thyroxine-binding, and cortisol-binding globulins. However, it has been found that after only 3 weeks' administration transdermally

administered estradiol elicits a dose-dependent reduction in urinary excretion of calcium and hydroxyproline.

An increase in HDL concentrations has been observed after 24 weeks' continuous administration of Estraderm TTS 100.

Studies conducted with Estraderm TTS and progestogen have indicated a lowering of serum total cholesterol, low density lipoprotein (LDL) and triglyceride levels, and an increase of high density lipoprotein (HDL) levels. Unopposed estrogens increase the incidence of endometrial hyperplasia and the risk of endometrial carcinoma. Studies have reported that the addition of a progestogen for 10 or more days of a cycle of estrogen administration greatly lowers the incidence of endometrial hyperplasia, and thereby irregular bleeding and endometrial carcinoma, compared to estrogen treatment alone.

Pharmacokinetic properties

Physiological serum estradiol concentrations, which are linearly proportional to the size of the dose, are attained within 4 hours after application of Estraderm TTS 25, 50 and 100 to the skin. Steady-state serum estradiol concentrations are reached within 8 hours after application of Estraderm TTS 25, 50, and 100 and are maintained at mean levels of 23, 40, and 75 pg/mL respectively during the remainder of the application period. This corresponds to mean increases of 16, 30, and 70 pg/mL of the postmenopausal baseline value (5-10 pg/mL). The E2:E1 ratio averages 0.9:1, 1:1, and 1.35:1, respectively.

24 hours after removal of the system, the estradiol concentrations in the serum have dropped almost to the baseline value. Estradiol conjugates excreted in the urine return to pre-application levels on the second or third day after removal of the system.

During repeated application of Estraderm TTS 50 twice weekly for 3 weeks (6 applications), mean serum concentrations of estradiol rise by 30 pg/mL and mean serum concentrations of estrone by 12 pg/mL. The average E2:E1 ratio changes from 1:5 to 0.9:1.

The amount of estradiol conjugates excreted in the urine remains elevated, at 2.0 to 2.5 micrograms/g creatinine throughout the period of application. Within 2 to 3 days after removal of the system, levels return to baseline, e.g. about 0.5 micrograms/g creatinine.

Estradiol

The plasma elimination half-life of estradiol is about 1 hour. Metabolic plasma clearance ranges from 650 to 900 L/(day x m²). Estradiol is mainly metabolised in the liver. Its most important metabolites are oestriol and oestrone and their glucuronides and sulfate conjugates; these are far less active than estradiol and are mainly excreted in the urine. Estrogen metabolites are also subject to enterohepatic circulation.

Preclinical safety data

At low physiological doses of estradiol (similar to those delivered by Estraderm TTS), neoplastic potential is negligible in experimental animals. Most of the documented effects of exogenously administered estradiol in animal studies have been consequences of the administration of supraphysiological doses and are consistent with an exaggerated pharmacological response (most notably the promotion of tumours in estrogen-responsive tissues). However, long-term unopposed treatment with physiological doses of estradiol may lead to hyperplastic changes in estrogen-dependent reproductive organs like the uterus.

A similar spectrum of tumour formation is known to occur in long-term laboratory animal studies with progestogen alone or in combination with estrogen with some species differences. However, results from clinical studies and epidemiological evidence on the carcinogenic risk to humans are addressed under the section (see. Special warnings and special precautions for use).

In local tolerability studies in rabbits, some skin irritation was observed.

Pharmaceutical particulars

List of excipients

Ethanol, hydroxypropylcellulose, polyethylene terephthalate, ethylenevinylacetate copolymer, liquid paraffin, polyisobutylene, silicone-coating on the inner side of the protective liner (removed before the application of the patch).

Incompatibilities

Ultraviolet light (e.g. sunlight)

Exposure of the Estraderm TTS patch to ultraviolet light results in degradation of estradiol. Patches should not be exposed to sunlight. They should be applied immediately after removal from the sachet to clothed skin sites.

Shelf life

2 years.

Special precautions for storage

Store below 25°C.

Estraderm TTS patches must remain in their pouch during storage.

Estraderm TTS should be kept out of the reach and sight of children.

Nature and contents of container

Estraderm systems are individually packaged in a heat-sealed sachet made of aluminum/Surllyn foil.

Medicine classification

Prescription Medicine

Name and address

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