NOVARTIS

Estraderm TTS®

COMPOSITION

Active substance: Oestradiol hemihydrate, equivalent to oestradiol (oestra-1,3,5(10)-triene-3,17ß-diol).
Excipients: Ethanol, hydroxypropylcellulose, polyethylene terephthalate, ethylene vinyl acetate copolymer, liquid paraffin, polyisobutylene, silicone coating on the inner side of the protective liner (removed before application of the patch).

PHARMACEUTICAL FORM AND QUANTITY OF ACTIVE SUBSTANCE PER UNIT

Transdermal patch
Estraderm TTS is a flat, transparent, multilayer transdermal therapeutic system (TTS), i.e. a patch for application to an area of intact skin.
The drug reservoir is sealed between a strengthened layer and a membrane that controls the rate at which oestradiol is continually released across the adhesive layer into the skin. The active substance penetrates the skin and passes directly into the bloodstream.
The following three systems are available:

	Estraderm TTS 25	Estraderm TTS 50	Estraderm TTS 100
Nominal rate of oestradiol release	25 µg/day	50 µg/day	100 µg/day
Oestradiol content	2 mg	4 mg	8 mg
Drug-releasing area	5 cm^2	10 cm^2	20 cm^2
Imprint (on backing film)	CG DWD	CG EFE	CG FBF
Shape	round	round	oblong

The rate of active substance release is maintained for a period of four days.

Indications/Potential uses

Treatment of signs and symptoms of oestrogen deficiency due to natural or surgically induced menopause, e.g. hot flushes, sleep disturbances, urogenital atrophy, and accompanying mood changes.
Prevention of accelerated postmenopausal bone loss, which can lead to osteoporosis.
In women with an intact uterus, oestrogen replacement therapy must always be supplemented by administration of a progestogen.

DOSAGE AND ADMINISTRATION

For all therapeutic indications, the lowest effective dose should always be used. Hormone replacement therapy (HRT), involving either oestrogen alone or the combination of oestrogen and progestogen, should only be continued as long as the benefits outweigh the risks for the individual patient.

Dosage

Estraderm TTS is applied twice weekly, i.e. the patch should be changed every 3–4 days.
Treatment is usually started with Estraderm TTS 50.
In the further course of treatment the dosage should be adjusted to the individual patient's needs. Breast discomfort, breakthrough bleeding, fluid retention or bloating persisting for more than about 6 weeks are generally signs that the dose is too high and needs to be reduced. If, on the other hand, the dose selected fails to eliminate the signs and symptoms of oestrogen deficiency, a higher dose should be given. For treatment of menopausal symptoms the lowest effective dose should always be used.
For the prevention of accelerated bone loss, Estraderm TTS 50 or 100 is recommended. Estraderm TTS 25 should only be prescribed for women who cannot tolerate a higher dose. Epidemiological data indicate that, when given for at least 5 years early in the menopause, oestrogen replacement therapy reduces subsequent hip and femoral neck fractures by about 50% and vertebral fractures by up to 90%.
Estraderm TTS is administered as continuous treatment (uninterrupted application twice weekly).
In women with an intact uterus, oestrogen replacement must be supplemented by sequential administration of a progestogen (e.g. 10 mg medroxyprogesterone acetate, 5 mg norethisterone, 1–5 mg norethisterone acetate, or 20 mg dydrogesterone per day) for at least the last 12 days of a 4 week treatment cycle.
Withdrawal bleeding usually occurs following the 12 days or more of progestogen therapy.

Administration

Method of administration
Immediately after removal of the protective liner, the Estraderm TTS patch should be applied to an area of clean, dry, intact skin.

This should be a site at which little wrinkling of the skin occurs during movement (e.g. buttock, hip, abdomen) and which is not exposed to sunlight (i.e. an area normally covered by clothing).
Experience to date has shown that less irritation of the skin occurs following application to the buttocks than at other sites. It is therefore advisable to apply Estraderm TTS to the buttock.
The site selected should be non-greasy and free of irritation.
Estraderm patches must not be applied to the breasts. They should not be applied to the same site twice in succession.
If a woman has forgotten to apply a patch, she should put on a new one as soon as possible. The next patch should be applied according to the original treatment schedule. Interrupting treatment might increase the likelihood of a recurrence of symptoms of breakthrough bleeding and spotting.

CONTRAINDICATIONS

Estraderm TTS must not be used in the following cases:
Known or suspected breast cancer
Known or suspected endometrial carcinoma or other oestrogen-dependent neoplasia
Abnormal vaginal bleeding, the cause of which has not been diagnosed
Severe liver disease
History of, or current, venous thromboembolic disease (e.g. deep vein thrombosis, pulmonary embolism)
Known coagulation disorders or thrombophlebitis
History of, or current, arterial thromboembolic disease (e.g. angina pectoris, myocardial infarction, stroke)
Porphyria.
Known hypersensitivity to oestrogen or any other component of Estraderm TTS
Known or suspected pregnancy
Lactation

WARNINGS AND PRECAUTIONS

Before initiating or reinstituting HRT, a complete individual and family medical history should be taken and a physical examination (including pelvic organs and breast) performed. During treatment, periodic check-ups should be carried out. Risks for women treated with HRT should be carefully appraised on a regular basis and the need for HRT should be reevaluated (also see **Contraindications**).
Consideration should always be given to the lowest effective dose and the shortest possible duration of treatment.

Osteoporosis

When initiating HRT for the prevention of osteoporosis, particularly careful consideration should be given to each woman's individual risk-benefit ratio. Potential alternative therapies should be considered if the risks outweigh the benefits. Periodic reevaluation is recommended during continuous treatment.

Contact sensitization

Contact sensitization is known to occur with all topical applications. In the very rare event of contact sensitization to one of the components of the patch, women should be warned that continued exposure to the causative agent may lead to a severe hypersensitivity reaction.

Cardiovascular disease

HRT should not be used to prevent cardiovascular disease.
Large-scale clinical trials (Women's Health Initiative [WHI] and Heart and Estrogen/Progestin Replacement study [HERS]) have shown an increased cardiovascular risk in women treated with the combined HRT products studied.
Risk assessment for unopposed oestrogen therapy has not yet been concluded.
In the large-scale, randomized WHI clinical study, women on continuous combined oral conjugated equine oestrogens (CEE) and medroxyprogesterone acetate (MPA) were monitored for an average of 5.2 years. In this study, the absolute excess risk of cardiovascular disease in women on HRT was 7 additional cases per 10 000 persons per year (37 vs 30), and the relative risk was 1.29.
In addition, the WHI study showed an increased incidence of stroke. The absolute excess risk in women on HRT was 8 additional cases per 10 000 persons per year (29 versus 21), and the relative risk was 1.41.
HERS, a controlled clinical study of secondary prevention in postmenopausal women with documented heart disease, was carried out using CEE and MPA. It showed an increased risk of cardiovascular events in the first year of treatment and no cardiovascular benefit thereafter.
To date there have been no randomized, controlled trials to assess the risk of stroke or cardiovascular morbidity and mortality associated with transdermal HRT products containing combinations of oestrogen and progestogen. There are therefore no data to support the conclusion that the frequency of cardiovascular events or stroke is different with Estraderm TTS.

Thromboembolic disease

HRT with either oestrogen or combined oestrogen-progestogen is associated with an elevated risk of venous thromboembolism (VTE), e.g. deep venous thrombosis or pulmonary embolism.
Two randomized controlled trials (WHI and HERS) and epidemiological studies showed the risk for women on HRT to be two to three times higher than for women not on HRT.
The WHI study showed an increased incidence of pulmonary embolism. The absolute excess risk in women on HRT was 8 additional cases per 10 000 persons per year (15 vs 7), and the relative risk was 2.13.
This elevated risk was found only in women on HRT, not in former HRT patients. The risk appears to be higher in the first years of use.
For non-users, the incidence of VTE over a 5 year period is estimated to be about 3 per 1000 for women aged 50–59 years and 8 per 1000 for women aged 60–69 years. It is estimated that in healthy women on HRT for 5 years, there are between 2 and 6 additional cases of VTE per 1000 for women aged 50–59 years and between 5 and 15 additional cases of VTE per 1000 for women aged 60–69 years.
The individual risk-benefit ratio should be carefully weighed in consultation with the patient if HRT is to be carried out in women with a risk factor for VTE not already mentioned in the **Contraindications** section.
Generally recognized risk factors for VTE include a personal or family history of thromboembolic disease (the occurrence of VTE in a close relative at an early age may indicate genetic predisposition), smoking, severe obesity (body mass index >30 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 abortion 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 if there is prolonged immobilization, major elective or post-traumatic surgery or major trauma.
In women on HRT scrupulous attention should be given to prophylactic measures to prevent VTE following surgery.
Depending on the type of surgery and the duration of immobilization, consideration should be given to temporarily stopping HRT, if possible a few weeks prior to the operation. Treatment should not be reinitiated until the woman is completely mobile.
Patients 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 chest pain, dyspnoea).
If VTE develops after the start of therapy the drug should be discontinued immediately.

Breast cancer

Randomized controlled trials and epidemiological studies have shown an increased risk of breast cancer in women using HRT over several years. The risk may have been higher in women using combined oestrogen-progestogen HRT than in women using only oestrogens. The additional risk increases with the duration of combined oestrogen-progestogen treatment.
The WHI study showed that the additional risk of breast cancer in women on combined HRT was 8 additional cases per 10 000 persons per year (38 versus 30). The relative risk was 1.26.
A meta-analysis was carried out on 51 epidemiological studies conducted between the 1970s and the early 1990s. It showed that women who had never received HRT had the lowest risk of breast cancer. The cumulative incidence of breast cancer in women between the ages of 50 and 70 was about 45 per 1000 women. It is assumed that in women currently or formerly on HRT for 5, 10 and 15 years, the number of additional diagnosed breast cancer cases is 2, 6, and 12, respectively.
The number of additional cases of breast cancer is similar for all women who start HRT, regardless of their age at the start of treatment (between 45 and 65).
The additional risk seems to decline again within five years of stopping HRT.
To date there have been no randomized, controlled trials to assess the risk of breast cancer associated with transdermal HRT products containing oestrogen or combinations of oestrogen and progestogen. There are nonetheless no data to support the conclusion that the frequency of breast cancer is different with Estraderm TTS.
Patients should therefore be instructed to inform their doctors of any changes in their breasts. Medical examinations, including mammography, should be carried out in accordance with currently accepted examination practices, but modified according to the clinical needs of the individual patient.

Endometrial cancer

The risk of endometrial cancer in women with an intact uterus is higher with unopposed oestrogen therapy than without oestrogen therapy; it appears to be dependent on treatment duration and oestrogen dosage. The greatest risk appears to be associated with long-term use.
Appropriate coadministration of a progestogen has been shown to reduce the incidence of endometrial hyperplasia and thus the potential risk of endometrial cancer associated with long-term oestrogen therapy.

Endometriosis

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

Haemorrhage

In all cases of persistent heavy or irregular vaginal bleeding or spotting of unknown cause, adequate diagnostic measures, including endometrial sampling if indicated, should be undertaken to rule out abnormality, and the appropriateness of therapy should be reassessed.
The cause of breakthrough bleeding or spotting must be investigated. An endometrial biopsy may be necessary to exclude the possibility of endometrial anomalies. HRT should then be reassessed.

Ovarian cancer

Some epidemiological studies have shown an increased risk of ovarian cancer in hysterectomized women on long-term HRT with unopposed oestrogens.

Risk factors for oestradiol-dependent tumours

Caution is advised when there are risk factors for oestrogen-dependent tumours (e.g. first-degree blood relatives who have had breast cancer).
Hysterectomized women for whom postmenopausal hormone therapy is suitable should receive unopposed oestrogen therapy unless other treatment is indicated (e.g. in patients with endometriosis).

Exacerbation or recurrence of symptoms with oestrogens

The patient must be closely monitored if any of the following conditions occur, or have occurred previously and/or during pregnancy or previous hormone treatment: leiomyoma (uterine fibroids) or endometriosis, risk factors for thromboembolic disease, heart failure, hypertension, hepatic disease (e.g. liver adenoma), renal disease, diabetes mellitus with or without vascular involvement, cholelithiasis, migraine or severe headache, systemic lupus erythematosus, endometrial hyperplasia, epilepsy, asthma, otosclerosis, gallbladder disease, oestrogen-related jaundice, pruritus.
It must be taken into account that such conditions may recur or be aggravated during treatment with oestrogens.

Reasons for immediate withdrawal of treatment

Treatment should be discontinued in the following cases: jaundice or deterioration of liver function, a significant increase in blood pressure, new onset of migraine-type headache, pregnancy, or any condition described in the **Contraindications** section.

Fluid retention

Oestrogens may cause fluid retention, and women with cardiac or renal dysfunction must therefore be carefully monitored.

Hypertriglyceridaemia

Women with hypertriglyceridaemia should be closely monitored during oestrogen HRT because there have been rare reports of marked increases in plasma triglycerides leading to pancreatitis during oral oestrogen therapy.

Diabetes

Although observations to date suggest that oestrogens, including transdermally applied oestradiol, and low doses of transdermal progestogens do not impair carbohydrate metabolism, diabetic patients should be closely monitored at the start of therapy until further data are available.

Fertility

Patients should be informe
a contraceptive and will no
If exacerbation of any of th
factors occurs or is suspec
and risks of HRT should be
basis.

INTERACTIONS

Metabolism of oestrogens
comitant administration of
convulsants (e.g. phenobar
mazepine), meprobamate,
infectives (e.g. rifampicin,
efavirenz) – known to indu
enzymes, in particular cyto
Caution is required when c
protease inhibitors (e.g. rit
are known to be strong inhi
enzymes but which exhibit
used concomitantly with st
Herbal preparations contain
perforatum) may induce th
Clinically, increased metab
progestogens may lead to c
changes in the uterine blee
With transdermal HRT, the
is avoided. Transdermally a
fore be less affected by enz
administered hormones.

PREGNANCY AND LACTA

Estraderm TTS must not b
pregnant or breastfeeding.
There is no indication for E
are pregnant or breastfeedi

EFFECTS ON ABILITY TO

No relevant studies have be

ADVERSE EFFECTS

Frequency

Very common: ≥ 10%; con
uncommon: ≥ 0.1 to <1%
very rare: < 0.01%

Nervous system

Common: Headache.
Uncommon: Migraine.
Rare: Dizziness.

Cardiovascular system

Very rare: Thromboembolic
of varicose veins, hyperten

Gastrointestinal tract

Common: Nausea, abdomi
Very rare: Abnormal liver fu
jaundice.

to exclude the possibility of endometrial anomalies. HRT should then be reassessed.

Ovarian cancer
Some epidemiological studies have shown an increased risk of ovarian cancer in hysterectomized women on long-term HRT with unopposed oestrogens.

Risk factors for oestradiol-dependent tumours
Caution is advised when there are risk factors for oestrogen-dependent tumours (e.g. first-degree blood relatives who have had breast cancer).
Hysterectomized women for whom postmenopausal hormone therapy is suitable should receive unopposed oestrogen therapy unless other treatment is indicated (e.g. in patients with endometriosis).

Exacerbation or recurrence of symptoms with oestrogens
The patient must be closely monitored if any of the following conditions occur, or have occurred previously and/or during pregnancy or previous hormone treatment: leiomyoma (uterine fibroids) or endometriosis, risk factors for thromboembolic disease, heart failure, hypertension, hepatic disease (e.g. liver adenoma), renal disease, diabetes mellitus with or without vascular involvement, cholelithiasis, migraine or severe headache, systemic lupus erythematosus, endometrial hyperplasia, epilepsy, asthma, otosclerosis, gallbladder disease, oestrogen-related jaundice, pruritus.
It must be taken into account that such conditions may recur or be aggravated during treatment with oestrogens.

Reasons for immediate withdrawal of treatment
Treatment should be discontinued in the following cases: jaundice or deterioration of liver function, a significant increase in blood pressure, new onset of migraine-type headache, pregnancy, or any condition described in the **Contraindications** section.

Fluid retention
Oestrogens may cause fluid retention, and women with cardiac or renal dysfunction must therefore be carefully monitored.

Hypertriglyceridaemia
Women with hypertriglyceridaemia should be closely monitored during oestrogen HRT because there have been rare reports of marked increases in plasma triglycerides leading to pancreatitis during oral oestrogen therapy.

Diabetes
Although observations to date suggest that oestrogens, including transdermally applied oestradiol, and low doses of transdermal progestogens do not impair carbohydrate metabolism, diabetic patients should be closely monitored at the start of therapy until further data are available.

Fertility
Patients should be informed that Estraderm TTS is not a contraceptive and will not restore fertility.
If exacerbation of any of the specified diseases or risk factors occurs or is suspected during HRT, the benefits and risks of HRT should be reassessed on an individual basis.

INTERACTIONS
Metabolism of oestrogens may be increased by concomitant administration of substances – such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepine), meprobamate, phenylbutazone and antiinfectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz) – known to induce drug-metabolizing enzymes, in particular cytochrome P450 enzymes.
Caution is required when concomitantly administering protease inhibitors (e.g. ritonavir and nelfinavir), which are known to be strong inhibitors of cytochrome P450 enzymes but which exhibit inducing properties when used concomitantly with steroid hormones.
Herbal preparations containing St. John's wort *(Hypericum perforatum)* may induce the metabolism of oestrogens.
Clinically, increased metabolism of oestrogens and progestogens may lead to decreased efficacy and changes in the uterine bleeding profile.
With transdermal HRT, the first-pass effect in the liver is avoided. Transdermally applied oestrogens may therefore be less affected by enzyme inducers than orally administered hormones.

PREGNANCY AND LACTATION
Estraderm TTS must not be used by women who are pregnant or breastfeeding.
There is no indication for Estraderm TTS in women who are pregnant or breastfeeding.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
No relevant studies have been carried out.

ADVERSE EFFECTS
Frequency
Very common: ≥ 10%; common: ≥ 1 to <10%; uncommon: ≥ 0.1 to <1%; rare: ≥ 0.01% to <0.1%; very rare: < 0.01%

Nervous system
Common: Headache.
Uncommon: Migraine.
Rare: Dizziness.

Cardiovascular system
Very rare: Thromboembolic disturbances, exacerbation of varicose veins, hypertension.

Gastrointestinal tract
Common: Nausea, abdominal cramps, bloating.
Very rare: Abnormal liver function tests, cholestatic jaundice.

Skin and subcutaneous tissue
Very common: Transient erythema and irritation at the site of application, with or without pruritus.
Very rare: Contact dermatitis; pigmentation disorders, generalized pruritus and rash.

Reproductive system and breast disorders
Very common: Breast discomfort (sign of oestrogen effect or, possibly, overdosage), breakthrough bleeding (usually a sign of oestrogen overdosage; if the oestrogen is adequately combined with a [sequential] progestogen, there is usually withdrawal bleeding as in a normal menstrual cycle).
Like any oestrogen therapy, transdermal oestrogen treatment can cause endometrial hyperplasia unless it is supplemented by adequate doses of a progestogen.
Uncommon: Breast cancer.

Other
Rare: Oedema, weight changes, pain in the legs (normally transient, lasting 3–6 weeks and unrelated to thromboembolic disease). If such disturbances persist, the dosage should be reduced.
Very rare: Anaphylactoid reactions (a history of allergy was reported in some patients).
Other adverse effects have been reported in association with HRT, including benign and malignant oestrogen-dependent neoplasms (e.g. endometrial cancer), venous thromboembolism (e.g. deep leg or pelvic venous thrombosis and pulmonary embolism), stroke, and myocardial infarction.

OVERDOSE
In view of the mode of administration, overdosage with oestradiol is unlikely, but can be rapidly reversed if necessary by removing the patch.
Symptoms of overdose: See **Adverse effects**.

Properties and Actions
Oestrogens
ATC Code G03 CA03

Oestradiol
Like all steroid hormones, oestrogens exert their metabolic effects intracellularly. In the cells of target organs, oestrogens interact with a specific receptor to form a complex which stimulates DNA and protein synthesis. Such receptors have been identified in various organs – e.g. hypothalamus, pituitary, vagina, urethra, uterus, breast and liver – and in osteoblasts.
Oestradiol, which from the menarche to the menopause is produced mainly by the ovarian follicles, is the most effective oestrogen. After the menopause, when the ovaries have ceased to function, only small amounts of oestradiol are still produced, by aromatization of androstenedione and to a lesser extent of testosterone by the enzyme aromatase, yielding oestrone and oestradiol, respectively. Oestrone is further transformed into oestradiol by the enzyme 17ß-hydroxysteroid dehydrogenase. Both enzymes occur primarily in fat, liver and muscle tissue.
In many women, cessation of ovarian oestradiol production results in vasomotor and thermoregulatory symptoms (hot flushes), sleep disturbances and progressive atrophy of the urogenital system. These disturbances can be largely eliminated by means of oestrogen replacement therapy.
When given at the appropriate dosage, oestrogen replacement therapy has been shown to prevent postmenopausal bone loss, particularly when it is introduced early in the menopause.
Transdermal therapy with Estraderm TTS delivers the physiological oestrogen, oestradiol, in unchanged form directly into the bloodstream. Oestradiol concentrations are raised to levels similar to those in the early follicular phase and are maintained over the application period of 3–4 days. The concentration ratio of oestradiol (E_2) to oestrone (E_1) in the plasma undergoes a corresponding shift from between 1:5–1:2 to approx. 1:1, i.e. to values similar to those measured before the menopause in women with normally functioning ovaries. Estraderm TTS thus provides physiological oestrogen replacement.
Following application of Estraderm TTS over a period of 28 days, no effect was observed on the concentration or activity of the blood coagulation factors fibrinopeptide A, high-molecular-weight fibrinogen or antithrombin III. At the end of this period, transdermally applied oestradiol was shown to have no effect on concentrations of circulating renin substrate or of the sex-hormone-binding, thyroxine-binding and cortisol-binding globulins. However, it was demonstrated that after only 3 weeks' transdermal administration, oestradiol elicits a dose-dependent reduction in urinary excretion of calcium and hydroxyproline.
An increase in high-density lipoprotein (HDL) levels was observed 24 weeks after continuous application of Estraderm TTS 100.
Studies with Estraderm TTS and progestogen have shown a reduction in total serum cholesterol, low density lipoproteins (LDL) and triglycerides, and an increase in high density lipoproteins (HDL).
Use of oestrogens alone increases the incidence of endometrial hyperplasia and the risk of endometrial carcinoma.
Studies have shown that the addition of a progestogen for 10 or more days of a cycle of oestrogen administration greatly lowers the incidence of endometrial hyperplasia, and thus also of irregular bleeding and endometrial carcinoma, compared to oestrogen therapy alone.

PHARMACOKINETICS
Estraderm TTS
Absorption
Physiological serum oestradiol concentrations that are linearly proportional to the size of the dose are reached within four hours of application of Estraderm TTS 25, 50 or 100 to the skin.

Distribution
Steady-state serum oestradiol concentrations are reached within 8 hours after application of Estraderm TTS 25, 50 or 100, and are maintained at a plateau level of 23, 40 or 75 pg/ml, respectively, for the duration of application.
This corresponds to a mean increase of 16, 30 or 70 pg/ml, respectively, above the baseline values which, after menopause, lie between 5 and 10 pg/ml. The mean E_2:E_1 ratio is 0.9:1, 1:1 and 1.35:1, respectively.
Serum oestradiol concentrations return almost to the baseline level within 24 hours of patch removal.
With twice weekly application of Estraderm TTS 50 for 3 weeks (total of 6 patches), the mean serum concentration of oestradiol is increased by 30 pg/ml and that of oestrone by 12 pg/ml. The mean E_2:E_1 ratio changes from 1:5 to 0.9:1.

Elimination
The urinary excretion rate of the oestradiol conjugates returns to the baseline level within 2–3 days after patch removal.
Urinary excretion of oestradiol conjugates is consistently raised during application and amounts to 2.0–2.5 µg/g creatinine. Following patch removal, it returns to the baseline level of 0.5 µg/g creatinine within 2–3 days.

Oestradiol
Metabolism
Oestradiol is primarily metabolized in the liver. Its main metabolites are oestriol, oestrone and their glucuronide and sulphate conjugates; these are far less active than oestradiol, however.

Elimination
The plasma elimination half-life of oestradiol is approx. 1 hour. Metabolic plasma clearance ranges from 650 to 900 litres/(day × m^2).
Excretion of the conjugates is primarily via the urine.
Oestrogen metabolites are also subject to enterohepatic circulation.

Preclinical data
The toxicity profile of oestradiol is well known. Aside from the data already specified in other sections of this prescribing information, there are no further preclinical data that are relevant to the prescribing physician.

OTHER INFORMATION
Incompatibilities
Ultraviolet light (i.e. sunlight)
Exposure of the Estraderm TTS patch to ultraviolet light results in degradation of oestradiol. The patches should therefore not be exposed to sunlight. They should be applied immediately after removal from the sachet to skin sites normally covered by clothing.

Special precautions for storage
Estraderm TTS should not be stored above 25°C. It must not be stored in a refrigerator.
The patches are individually packed in heat-sealed sachets made of aluminium/Surlyn foil and must remain in their intact sachets during storage.

Note
Used and unused Estraderm TTS patches should be kept out of the reach and sight of children.

PACK SIZES
Country specific pack sizes.

MANUFACTURER
See folding box.

Information last revised : May 2003
Approval date (text) : 14 July 2003

® = registered trademark

Novartis Pharma AG, Basle, Switzerland

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

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