# Product Monograph

## PrESTALIS®

(Norethindrone Acetate and Estradiol-17ß)

140/50 and 250/50 µg/day

## PrESTALIS-SEQUI®

(Estradiol-17ß and Norethindrone Acetate + Estradiol-17ß)

[supplied in packs containing 4 Vivelle® 50 and 4 Estalis® 140/50 or 4 Estalis 250/50 patches]

Transdermal Therapeutic Systems

Progestin- Estrogen

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**Warning**

As the Women's Health Initiative (WHI) study results indicated increased risk of myocardial infarction (MI), stroke, invasive breast cancer, pulmonary emboli and deep venous thrombosis in postmenopausal women receiving treatment with combined oral conjugated equine estrogens (CE 0.625 mg) and medroxyprogesterone acetate (MPA 2.5 mg) compared to those receiving placebo tablets, the following should be highly considered:

- Estrogens with or without progestins **should not** be prescribed for primary or secondary prevention of cardiovascular diseases.
- Estrogens with or without progestins should be prescribed at **the lowest effective dose** for the approved indications.
- Estrogens with or without progestins should be prescribed for **the shortest period** possible for the recognized indications.

# ACTION AND CLINICAL PHARMACOLOGY

ESTALIS (norethindrone acetate (NETA)/estradiol-17ß) is designed to provide continuous estrogen and progestin therapy, in a 28-day treatment cycle in women with an intact uterus.

ESTALIS-SEQUI (estradiol-17ß and NETA/estradiol-17ß) is designed to provide continuous estrogen and sequential progestin therapy, in a 28-day treatment cycle, for women with an intact uterus.

Transdermally delivered estradiol is metabolized only to a small extent by the skin and by-passes the first pass effect seen with orally administered estrogen products. Therapeutic estradiol serum levels with lower circulating levels of estrone and estrone conjugates are achieved with smaller transdermal doses (daily and total) as compared to oral therapy and more closely approximate premenopausal concentrations.

In a pharmacokinetic study, it was shown that ESTALIS matrix transdermal delivery system achieves estradiol serum levels and estrone to estradiol ratios in the range of those observed in premenopausal women at the early (estradiol >40 pg/mL) to mid-follicular phase. These features are maintained for an entire 84 to 96 hour wear period. Multiple applications of ESTALIS (250/50 µg/day, 140/50 µg/day) matrix transdermal delivery system resulted in average estradiol serum concentrations at steady-state of 50 and 45 pg/mL, respectively. At the end of the application periods, the average estradiol serum concentrations were 37 and 27 pg/mL, respectively. Estradiol has a short elimination half-life of approximately 2 to 3 hours. Therefore, a rapid decline in serum levels is observed after the matrix transdermal delivery system is removed. After removal of the matrix transdermal delivery system, serum concentrations of estradiol return to untreated postmenopausal levels (<20 pg/mL) within 4 - 8 hours.

In a pharmacokinetic study it was shown that multiple applications of ESTALIS (250/50 µg/day, 140/50 µg/day) matrix transdermal delivery systems resulted in average norethindrone serum concentrations at steady-state of 840 and 489 pg/mL, respectively. At the end of the application period, the average serum concentrations of norethindrone were 686 and 386 pg/mL, respectively. Serum norethindrone concentrations of ESTALIS increased linearly with increasing doses of NETA. The elimination half-life of norethindrone is reported to be 6 to 8 hours. After removal of the ESTALIS matrix transdermal delivery system, norethindrone serum concentrations diminish rapidly and are less than 50 pg/mL within 48 hours.

Minimal fluctuations in serum estradiol and norethindrone concentrations demonstrate consistent deliveries over the application interval. There is no accumulation of estradiol or norethindrone in the circulation following multiple applications.

## PIVOTAL CLINICAL TRIALS

### Treatment of vasomotor symptoms

Efficacy and safety of ESTALIS in the relief of menopausal and postmenopausal symptoms have been studied in two 3-month multicenter, randomized, double-blind, placebo-controlled, parallel group studies. A total of 446 non-hysterectomized healthy postmenopausal women with moderate-to-severe vasomotor symptoms (≥ 8 hot flushes/day of moderate-to-severe intensity with sweating) were enrolled in the studies 303 and 304. Over 3 months (3 cycles of 28 days), the study systems were applied on the skin twice weekly. In study 303, patients received ESTALIS as a continuous regimen (50 µg/day estradiol in combination with either 140 or 250 µg/day norethindrone acetate), whereas in study 304, patients received ESTALIS in a sequential regimen (50 µg/day estradiol only (VIVELLE) for the first 14 days of each 28-day cycle followed by 50 µg/day estradiol in combination with either 140 or 250 µg/day norethindrone acetate for the remaining 14 days of each 28-day cycle).

In both studies 303 and 304, ESTALIS was better than placebo in reducing the number of hot flushes per day from baseline to endpoint ($p<0.001$), as well as reducing the intensity of hot flushes ($p<0.001$) and sweating ($p<0.001$). In studies 303 and 304 combined, the discontinuation rate was 8%. In the ESTALIS 140/50 and 250/50 groups, the discontinuation rate due to adverse events was 4.5% compared to 2% in the placebo group.

### Protection against endometrial hyperplasia

ESTALIS was effective in reducing the incidence of estrogen-induced endometrial hyperplasia after 1 year of therapy in two Phase II clinical trials. Nine hundred fifty-five (955) postmenopausal women (with intact uteri) were treated with (i) a continuous regimen of ESTALIS alone *(Continuous Combined* regimen), (ii) a sequential regimen with an estradiol-only transdermal system (VIVELLE) followed by an ESTALIS transdermal system (*Continuous Sequential* regimen) or (iii) continuous regimen with an estradiol-only transdermal system. The incidence of endometrial hyperplasia (primary endpoint) was significantly less after 1 year of therapy with either ESTALIS regimen than with the estradiol-only transdermal system (1% or less vs 35-70%, $p<0.001$). A regular and predictable bleeding pattern occurred in approximately two-thirds of women in each of the sequential regimen (ESTALIS + VIVELLE) groups. By comparison, the estrogen-only group had an increasing incidence of unpredictable irregular bleeding and spotting which contributed to the higher dropout rate of 37% for this group.

### Information regarding lipid effects

There are possible additional risks that may be associated with the inclusion of a progestin in estrogen replacement regimens. The potential risks include adverse effects on carbohydrate and lipid metabolism, mood changes and edema. The choice and dose of progestin may be important in minimizing these adverse effects and may differ among women.

One year clinical trials show that the ESTALIS transdermal delivery system decreases plasma LDL-cholesterol, total cholesterol, apolipoprotein B, high density lipoprotein-cholesterol (HDL-C), Lipoprotein(a),and triglycerides. Significantly greater reductions in LDL-cholesterol concentrations

and triglycerides were achieved as compared to continuous transdermal estradiol-alone. Changes in mean total cholesterol / HDL-C ratios were minimal after 1 year of treatment.

## INDICATIONS AND CLINICAL USE

ESTALIS (NETA/estradiol-17ß) and ESTALIS-SEQUI (estradiol-17ß and NETA/estradiol-17ß) are indicated for the relief of menopausal and postmenopausal symptoms occurring in naturally or surgically induced estrogen deficiency states e.g. hot flushes, sleep disturbances and vulvar and vaginal atrophy.

ESTALIS and ESTALIS-SEQUI are recommended for the above indication only in patients with an intact uterus since the regimen includes a progestin whose role is to prevent endometrial hyperplasia.

## CONTRAINDICATIONS

ESTALIS (NETA/estradiol-17ß) and ESTALIS-SEQUI (estradiol-17ß and NETA/estradiol-17ß) should not be administered to patients with any of the following conditions:

- Personal history of known or suspected estrogen-dependent neoplasia such as breast or endometrial cancer
- Known or suspected pregnancy
- Breast-feeding
- Endometrial hyperplasia
- Undiagnosed abnormal vaginal bleeding
- Porphyria
- Active or past history of arterial thromboembolic disease (eg.cerebrovascular accident, myocardial infarction, coronary heart disease)
- Active or past history of confirmed venous thromboembolism (such as deep venous thrombosis or pulmonary embolism) or active thrombophlebitis
- Active hepatic dysfunction or disease, especially of the obstructive type
- Severe hepatic disease
- Classical migraine
- Partial or complete loss of vision from ophthalmic vascular disease
- Known or suspected hypersensitivity to any component of the patch

# WARNINGS

See **Boxed Warning** at the front page.

## CARDIOVASCULAR DISORDERS

Available epidemiological disorders data indicate that use of estrogen with or without progestin is associated with an increased risk of stroke and coronary heart disease. WHI-trial's results concluded that there are more risks than benefits among women using combined Hormone Replacement Therapy (HRT), compared to the group using placebo. In 10,000 women on combined oral HRT (conjugated equine estrogens/medroxyprogesterone acetate) over one year period, there were seven more cases of coronary heart disease (37 on combined HRT versus 30 on placebo) and eight more cases of strokes (29 versus 21).

In the Heart and Estrogen/progestin Replacement Study (HERS) of postmenopausal women with documented heart disease (n =2763, average age 66.7 years), a randomized placebo-controlled clinical trial of secondary prevention of coronary heart disease (CHD), treatment with 0.625 mg/day oral conjugated equine estrogen (CEE) plus 2.5 mg medroxyprogesterone acetate (MPA) demonstrated no cardiovascular benefit.

Specifically, during an average follow-up of 4.1 years, treatment with CEE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the hormone-treated group than in the placebo group in year 1, but not during the subsequent years.

From the original HERS trial, 2321 women consented to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. After 6.8 years, hormone therapy did not reduce the risk of cardiovascular events in women with CHD.

## BREAST CANCER

Current epidemiological data indicate that the use of combined HRT is associated with an increased risk of invasive breast cancer. WHI-trial's results suggest that risks exceed benefits among women using combined HRT (conjugated equine estrogens/medroxyprogesterone acetate), compared to the group using placebo. In 10,000 women on combined HRT over one year period, there were eight more cases of invasive breast cancer (38 on combined HRT versus 30 on placebo).

The WHI study reported that the invasive breast cancers diagnosed in the estrogen plus progestin group were similar in histology but were larger [mean (SD), 1.7 cm (1.1) vs 1.5 cm (0.9), respectively; P=0.04] and were at a more advanced stage compared with those diagnosed in the placebo group.

The WHI trial also reported that the percentage of women with abnormal mammograms (recommendations for short-interval follow-up, a suspicious abnormality, or highly suggestive of malignancy) was significantly higher in the oestrogen plus progestin group versus the placebo group. This difference appeared at year one and persisted in each year thereafter.

It is recommended that estrogens not be given to women with existing breast cancer or those with a previous history of the disease. There is a need for caution in prescribing estrogens for women with known risk factors associated with the development of breast cancer, such as strong family history of breast cancer (first degree relative) or who present a breast condition with an increased risk (breast nodules, fibrocystic disease of the breast, or abnormal mammograms and/or atypical hyperplasia at breast biopsy). Other known risk factors for the development of breast cancer such as nulliparity, obesity, early menarche, late age at first full term pregnancy and at menopause should also be evaluated.

It is recommended that women undergo mammography prior to the start of HRT treatment and at regular intervals during treatment, as deemed appropriate by the treating physician and according to the perceived risks for each patient.

The overall benefits and possible risks of hormone replacement therapy should be fully considered and discussed with patients. It is important that the increased risk of being diagnosed with breast cancer after 4 years of treatment with HRT (as reported in the results of WHI-trial) is discussed with the patient and weighed against its known benefits. **Instructions for self-examination of the breasts should be included in this counselling.**

## VENOUS THROMBOEMBOLISM

Recent epidemiological data indicate that the use of estrogen with or without progestin is associated with an increased risk of developing venous thromboembolism (VTE). WHI-trial's results suggest that risks exceed benefits among women using combined HRT (conjugated equine estrogens/medroxyprogesterone acetate), compared to the group using placebo. In 10,000 women on combined HRT over a period of one year, there were eighteen more cases of total blood clots in the lungs and legs (34 on combined HRT versus 16 on placebo).

Generally recognized risk factors for VTE include a personal history, a 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 $kg/m^2$), systemic lupus erythematosus (SLE) and severe varicose veins. The risk of VTE also increases with age and smoking.

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

The risk of VTE may be temporarily increased with prolonged immobilization, major elective surgery or posttraumatic surgery, or major trauma (if feasible, HRT should be discontinued at least 4 weeks before major surgery which may be associated with an increased risk of thromboembolism, or during periods of prolonged immobilization). The treatment should not be restarted until the woman is completely mobile. In women on HRT, attention should be given to prophylactic measures to prevent VTE following surgery Also, patients with varicose veins should be closely supervised although there is no consensus about the possible role of varicose veins in VTE. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, hormone therapy should be discontinued immediately.

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 pain in the chest, dyspnoea).

**ENDOMETRIAL HYPERPLASIA & ENDOMETRIAL CARCINOMA**

Estrogen-only HRT increases the risk of endometrial hyperplasia (if taken by women with intact uteri).

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 (**see Coadministration of Progestins under Dosage and Administration and Pharmacology**).

**OVARIAN CANCER**

In some epidemiological studies, the long-term use of unopposed estrogens in hysterectomised women has been associated with an increased risk of ovarian cancer. It is uncertain whether long-term use of combined HRT (estrogens and progestogens) confers a different risk than estrogen-only HRT products.

**GALLBLADDER DISEASES**

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving postmenopausal estrogens has been reported with combined oral CE and MPA treatment.

**CONTACT SENSITIZATION**

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

**BENIGN HEPATIC ADENOMAS AND HEPATOCELLULAR CARCINOMA**

Benign hepatic adenomas have been associated with the use of combined estrogen and progestin oral contraceptives. Although benign and rare, these tumours may rupture and cause death from intra-abdominal hemorrhage. Such lesions have not yet been reported in association with other estrogen or progestin preparations, but they should be considered if abdominal pain and tenderness, abdominal mass, or hypovolemic shock occurs in patients receiving estrogen. Hepatocellular carcinoma has also been reported in women taking estrogen-containing oral contraceptives. The causal relationship of this malignancy to these drugs is not known.

**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.

Since only women aged 65 and older were included in this study, 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 or estrogen-progestogen combined products, no large randomized 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 ESTALIS or ESTALIS-SEQUI.

## PRECAUTIONS

- Before ESTALIS OR ESTALIS-SEQUI (norethindrone acetate (NETA)/estradiol-17ß) is administered, the patient should have a complete physical examination including a blood pressure determination. Breasts and pelvic organs should be appropriately examined and a Papanicolaou smear should be performed. Endometrial biopsy should be done when indicated. Baseline tests should include mammography, measurements of blood glucose, calcium, triglycerides and cholesterol, and liver function tests.

- The first follow-up examination should be done within 3-6 months after initiation of treatment to assess response to treatment. Thereafter, examinations should be made at intervals at least once a year and should include at least those procedures outlined above.

- 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.

- **It is important that patients are encouraged to practice frequent self-examination of the breasts.**

- Abnormal vaginal bleeding, due to its prolongation, irregularity or heaviness, occurring during therapy should prompt diagnostic measures like endometrial biopsy or curettage to rule out the possibility of uterine malignancy and the treatment should be re-evaluated.

- Pre-existing uterine leiomyoma may increase in size during estrogen use. Growth, pain or tenderness of uterine leiomyoma requires discontinuation of medication.

- Symptoms and physical findings associated with a previous diagnosis of endometriosis may reappear or become aggravated with estrogen use.

- If feasible, HRT should be discontinued at least 4 weeks before major surgery which may be associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

- Patients who develop visual disturbances, classical migraine, transient aphasia, paralysis, or loss of consciousness should discontinue medication.

- Women using hormonal replacement therapy (HRT) sometimes experience increased blood pressure. Blood pressure should be monitored with HRT use. Elevation of blood pressure in previously normotensive or hypertensive patients should be evaluated and HRT therapy may have to be discontinued.

- Estrogens may cause fluid retention. Therefore, particular caution is indicated in cardiac or renal dysfunction, epilepsy or asthma. Treatment should be stopped if there is an increase

in epileptic seizures. If, in any of the above-mentioned conditions, a worsening of the underlying disease is diagnosed or suspected during treatment, the benefits and risks of treatment should be reassessed based on the individual case.

- Because the prolonged use of estrogens influences the metabolism of calcium and phosphorus, estrogens should be used with caution in patients with metabolic and malignant bone diseases associated with hypercalcemia, in patients with renal insufficiency and in patients with otosclerosis.

- A worsening of glucose tolerance and lipid metabolism have been observed in a significant percentage of peri- and post-menopausal patients on oral estrogen treatment. Therefore, diabetic patients or those with a predisposition to diabetes should be observed closely to detect any alterations in carbohydrate or lipid metabolism, especially in triglyceride blood levels.

- Caution is advised in patients with a history of estrogen-related jaundice and pruritus. If cholestatic jaundice develops during treatment, the treatment should be discontinued and appropriate investigations carried out.

- Women with familial hypertriglyceridemia need special surveillance. Lipid-lowering measures are recommended additionally, before treatment is started.

- Liver function tests should be done periodically in subjects who are suspected of having hepatic disease. For information on endocrine and liver function tests, see the section under **Laboratory Tests**.

## DRUG INTERACTIONS

Estrogens may diminish the effectiveness of anticoagulants, antidiabetic and antihypertensive agents.

Preparations inducing liver enzymes (e.g., barbiturates, hydantoins, carbamazepine, meprobamate, phenylbutazone or rifampicin) may interfere with the activity of orally administered estrogens.

The following section contains information on drug interactions with ethinyl estradiol-containing products (specifically, oral contraceptives) that have been reported in the public literature. It is unknown whether such interactions occur with drug products containing other types of estrogens.

1. The metabolism of ethinyl estradiol is increased by rifampicin and anticonvulsants such as phenobarbital, phenytoin and carbamazepine. Coadministration of troglitazone and certain ethinyl

estradiol containing drug products (e.g., oral contraceptives containing ethinyl estradiol) reduces the plasma concentrations of ethinyl estradiol by 30 percent.

Ascorbic acid and acetaminophen may increase AUC and/or plasma concentrations of ethinyl estradiol. Coadministration of atorvastatin and certain ethinyl estradiol containing drug products (e.g., oral contraceptives containing ethinyl estradiol) increases AUC values for ethinyl estradiol by 20 percent.

Clinical pharmacokinetics studies have not demonstrated any consistent effect of antibiotics (other than rifampicin) on plasma concentrations of synthetic steroids.

2. Drug products containing ethinyl estradiol may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporin, prednisolone, and theophylline have been reported with concomitant administration of certain drugs containing ethinyl estradiol (e.g., oral contraceptives containing ethinyl estradiol). In addition, these drugs containing ethinyl estradiol may induce the conjugation of other compounds.

Decreased plasma concentrations of acetaminophen and increased clearance of temazepam, salicylic acid, morphine and clofibric acid have been noted when these drugs were administered with certain ethinyl estradiol containing drug products (e.g., oral contraceptives containing ethinyl estradiol).

Concomitant administration of aminoglutethimide with medroxyprogesterone acetate (MPA) may significantly reduce the bioavailability of MPA.

It was found that some herbal products (e.g., St. John's wort) which are available as OTC products might affect metabolism, and therefore, efficacy and safety of estrogen/progestin products.

Physicians and other health care providers should be aware of other non-prescription products concomitantly used by the patients, including herbal and natural products obtained from the widely spread Health Stores.

**Laboratory Tests**

The results of certain endocrine and liver function tests may be affected by estrogen-containing products:

- increased sulfobromophthalein retention;
- increased prothrombin time and partial thromboplastin time; increased levels of fibrinogen and fibrinogen activity; increased coagulation factors VII, VIII, IX, X; increased norepinephrine-induced platelet aggregability; decreased antithrombin III;
- increased thyroxine-binding globulin (TBG), leading to increased circulating total thyroid hormone ($T_4$) as measured by column or radioimmunoassay; free $T_3$ resin uptake is decreased, reflecting the elevated TBG; free $T_4$ concentration is unaltered;

- other binding proteins may be elevated in serum i.e., corticosteroid binding globulin (CBG), sex-hormone binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively; free or biologically active hormone concentrations are unchanged;
- reduced response to the METOPIRONE test;
- impaired glucose tolerance;
- reduced serum folate concentration;
- increased serum triglyceride and phospholipid concentration.

With transdermally administered estradiol-17ß, no effect on fibrinogen, antithrombin III, TBG, CBG or SHBG and decreases in serum triglycerides have been observed.

The results of the above laboratory tests should not be considered reliable unless therapy has been discontinued for two to four months. The pathologist should be informed that the patient is receiving HRT when relevant specimens are submitted.

**Information To Be Provided To The Patient**

**See Information For The Consumer**.

## Adverse Reactions

**See Warnings and Precautions** regarding potential induction of malignant neoplasms and adverse effects similar to those of oral contraceptives.

The most commonly reported adverse reaction to ESTALIS (NETA/estradiol-17ß) in clinical trials was erythema at the application site. Less than 1% of patients treated sequentially and about 5% of patients treated continuously discontinued therapy due to an application site reaction. The most commonly reported adverse reaction to VIVELLE (estradiol-17ß) in clinical trials was redness and irritation at the application site. This caused approximately 0.8% of patients to discontinue therapy.

The following adverse reactions have been reported with estrogens in general.

**Gastrointestinal**

Nausea; vomiting; abdominal discomfort (cramps, pressure, pain); bloating; gallbladder disorder; asymptomatic impaired liver function; cholestatic jaundice.

**Genitourinary**

Breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea; vaginal itching/discharge; dyspareunia; dysuria; endometrial hyperplasia; pre-menstrual-like syndrome; reactivation of endometriosis; cystitis; changes in cervical erosion and amount of cervical secretion.

**Skin**

Allergic contact dermatitis; reversible post-inflammatory pigmentation; general pruritus and exanthema; loss of scalp hair; chloasma or melasma, which may persist when drug is discontinued; pigmentation of the skin; erythema nodosum; erythema multiforme; hemorrhagic skin eruptions; precipitation or aggravation of porphyria cutanea tarda in predisposed individuals and hirsutism.

Isolated cases of anaphylactoid reactions (some of the patients had a history of previous allergy or allergic disorders).

**Endocrine**

Breast swelling and tenderness; increased blood sugar levels; decreased glucose tolerance; sodium retention.

**Cardiovascular/Hematologic**

Palpitations; isolated cases of: thrombophlebitis; thromboembolic disorders; exacerbations of varicose veins; increase in blood pressure **(see Warnings and Precautions)**. Coronary thrombosis; altered coagulation tests **(see Laboratory Tests under Precautions)**.

**Central Nervous System**

Aggravation of migraine headaches; headaches; mental depression; nervousness; dizziness; fatigue; irritability; neuro-ocular lesions (e.g., retinal thrombosis, optic neuritis).

Dementia has been reported in association with some estrogen-progestogen treatments.

**Ophthalmic**

Visual disturbances; steepening of the corneal curvature; intolerance to contact lenses; neuro-ocular lesions **(see CNS above)**.

**Miscellaneous**

Changes in appetite; changes in body weight; edema; neuritis; change in libido; musculoskeletal pain [including leg pain not related to thromboembolic disease (usually transient, lasting 3-6 weeks). If symptoms persist, the dose of estrogen should be reduced].

If adverse symptoms persist, the prescription of HRT should be re-considered.

## Symptoms and Treatment of Overdosage

### Symptoms

Numerous reports of ingestion of large doses of estrogen products and estrogen-containing oral contraceptives by young children have not revealed acute serious ill effects. Overdosage with estrogen may cause nausea, breast discomfort, fluid retention, bloating or vaginal bleeding in women.

Progestin (norethindrone acetate) overdosage has been characterized by depressed mood, tiredness, acne and hirsutism.

### Treatment

Owing to the mode of administration (transdermal), plasma levels of estradiol-17ß and norethindrone acetate can be rapidly reduced by removal of the patch.

Symptomatic treatment should be given.

## Dosage And Administration

### Dosage

For initiation and maintenance of treatment, the lowest effective dose should always 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.

ESTALIS and ESTALIS-SEQUI are used as a continuous treatment (uninterrupted application twice weekly).

In women who are not currently taking oral estrogens, treatment with ESTALIS (NETA/estradiol-17ß) or ESTALIS-SEQUI (estradiol-17ß and NETA/estradiol-17ß) can be initiated at once. In

women who are currently taking oral estrogen, treatment with ESTALIS or ESTALIS-SEQUI can be initiated on reappearance of menopausal symptoms, following discontinuation of oral therapy.

**Therapeutic Regimens: Combination progestin/estrogen regimens are indicated for women with an intact uterus**. Two ESTALIS (NETA/estradiol-17ß) patches are available: 140 µg norethindrone acetate with 50 µg estradiol per day (9 $cm^2$) and 250 µg norethindrone acetate with 50 µg estradiol per day (16 $cm^2$). For all regimens, the requirement for hormone replacement therapy for menopausal symptoms should be reassessed periodically. Attempts to taper or discontinue the medication should be made at 3- to 6-month intervals.

***Continuous Combined Regimen**:*

ESTALIS 140/50 or ESTALIS 250/50 µg per day (16 $cm^2$) is worn continuously on the abdomen or buttocks. A new patch should be applied twice weekly during a 28-day cycle. Irregular uterine bleeding may occur particularly in the first 6 months, but generally decreases with time, and often to an amennorheic state.

If irregular uterine bleeding persists and uterine pathology has been ruled out by appropriate diagnostic measures, it may be more appropriate instead to prescribe Estalis using the sequential regimen described immediately below in order to make withdrawal uterine bleeding more regular and predictable.

***Sequential Regimen**:*

ESTALIS-SEQUI is used in a sequential regimen.

In this treatment regimen, VIVELLE 50 µg per day (nominal delivery rate) estradiol transdermal system is worn for the first 14 days of a 28-day cycle, replacing the system twice weekly. For the remaining 14 days of the 28-day cycle, ESTALIS 140/50 or ESTALIS 250/50 µg per day (16 $cm^2$) should be applied. The ESTALIS patch should be replaced twice weekly during this period in the cycle. Women should be advised that monthly withdrawal bleeding often occurs.

Figure 1

<table>
<tr><td>Week 1</td><td>  </td><td>  </td><td rowspan="2">VIVELLE 50 patch for the first 2 weeks</td></tr>
<tr><td>Week 2</td><td>  </td><td>  </td></tr>
<tr><td>Week 3</td><td>  </td><td>  </td><td>ESTALIS 140/50 or ESTALIS 250/50 patch for the following 2 weeks</td></tr>
</table>

| | | | |
|---|---|---|---|
| Week 4 | ◯ | ◯ | |

ESTALIS-SEQUI (estradiol-17ß followed by NETA/estradiol-17ß) provides, therefore, 14 days of progestin per cycle. The addition of sufficient NETA to induce secretory transformation of the endometrium during estrogen replacement therapy is mandatory.

As observed in the normal menstrual cycle, cyclical administration of NETA from ESTALIS 250/50 as recommended in the sequential regimen should induce REGULAR CYCLICAL bleeding with mean onset towards the end of the application phase. The normal duration of vaginal bleeding associated with sequential administration of ESTALIS is around 6 days. This cyclical bleeding is expected to be of light intensity or spotting for 60-70% of this time. There are individual variations in these parameters. Once all 4 patches of ESTALIS have been used as recommended, the first VIVELLE 50 patch of the new cycle is applied even if some vaginal bleeding still persists. Vaginal bleeding should stop early in the new cycle.

*Abnormal vaginal bleeding, due to its prolongation, irregularity or heaviness, in any patient receiving hormone replacement therapy requires institution of prompt diagnostic measures like endometrial biopsy or curettage to rule out the possibility of uterine malignancy.*

The short-term effects of NETA co-administration may include vaginal bleeding during or after NETA treatment, breast tenderness, and mood and weight changes. The long-term effects generally depend on the dosage and type of progestin used. The lowest effective dose of estrogen and progestin should be prescribed **(see Coadministration Of Progestins under Pharmacology)**.

**See the Precautions Section** on the examination of the patient before ESTALIS or ESTALIS-SEQUI administration.

**Patch Application**

The physician should discuss the most appropriate placement of the patch with the patient. Immediately after removal of a patch from the pouch and removal of one-half of the protective liner, the adhesive side of the ESTALIS or VIVELLE patch should be placed on a clean, dry area of intact skin and peel off the remaining one-half of the protective liner . The area selected should not be oily, damaged or irritated, and not exposed to the sun. The site selected should also be one at which little wrinkling of the skin occurs during movement of the body (buttocks and lower abdomen). The waistline should be avoided, since tight clothing may dislodge the patch. The patch should be pressed firmly in place with the palm of the hand for at least 10 seconds, making sure there is good contact, especially around the edges. In the event that a patch should fall off, it can be reapplied. If it fails to adhere then a new patch may be applied. In either case, the original treatment schedule should be continued. Patches should not be applied to the same skin site for at least one week.

**ESTALIS and VIVELLE must not be applied to the breasts to avoid potentially harmful effects on the breast tissue.**

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 and breakthrough bleeding and spotting.

**Children**

ESTALIS and ESTALIS-SEQUI should not be used in children.

# Pharmaceutical Information

**Drug Substance:**

**Estradiol USP (Estradiol-17ß):**

Description: White to creamy white, odorless, crystalline powder.

Chemical name: Estradiol hemihydrate

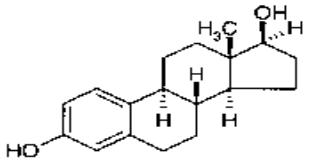
Estra-1,3,5(10)-triene-3,17$\beta$-diol.

Molecular weight: 281.4

Molecular formula: $C_{18}H_{24}O_2.½H_2O$

Structural Formula:

$_*$ ½ $H_2O$




Solubilities: Practically insoluble in water;
Soluble 1 in 28 of alcohol
Soluble 1 in 17 of acetone

**NORETHINDRONE ACETATE USP:**

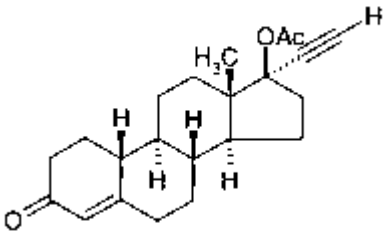
Description: White to creamy white, odorless, crystalline powder.

Chemical name: Norethindrone acetate
17-hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one acetate.

Molecular weight: 340.47

Molecular formula: $C_{22}H_{28}O_3$.

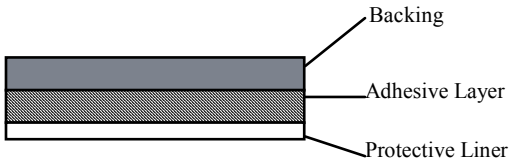
Structural Formula:




Solubilities: Insoluble in water;
Soluble 1 in 4 in acetone

Composition

**ESTALIS** is an alcohol-free, adhesive-based matrix transdermal patch comprising three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are: a backing, an adhesive layer, and a protective liner. The adhesive matrix containing 17$\beta$-estradiol and norethindrone acetate is applied to a polyester/ethylene vinyl acetate laminate film on one side and is protected on the other side by a transparent fluoropolymer coated release liner. The transparent release liner must be removed before the system can be used. Each patch is enclosed in a heat-sealed pouch.




ESTALIS 140/50 and 250/50 contain a fixed combination of norethindrone acetate (NETA) and estradiol-17ß. ESTALIS patches release controlled amounts of NETA and estradiol-17ß simultaneously through the skin for up to 4 days.

The active components of the system are estradiol USP and norethindrone acetate USP. The remaining components of the system are pharmacologically inactive; they are: a silicone (BIO PSA® X7-4603) and acrylic (Gelva® 737)-based multipolymeric adhesive, povidone USP, oleic acid NF, and dipropylene glycol.

**ESTALIS-SEQUI** contains two types of patches, VIVELLE 50 and ESTALIS 250/50 or ESTALIS 140/50. VIVELLE contains estradiol-17ß and ESTALIS contains norethindrone acetate (NETA) and estradiol-17ß.

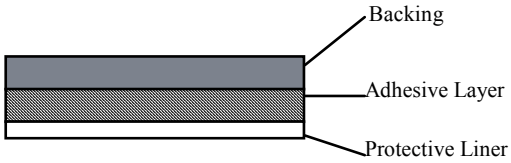
The first type of patch to be applied on the skin during the first 14 days of a 28-day treatment cycle is VIVELLE 50. VIVELLE 50 is a thin, circular, multilayer, transparent transdermal adhesive patch, containing estradiol-17ß that is designed for application to an area of intact skin.

The VIVELLE patch comprises three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are a backing film, an adhesive layer and a protective layer:

1. a flexible semi-transparent backing film of polyurethane and ethylene vinyl alcohol polymer.

2. an adhesive formulation containing estradiol-17ß, acrylic polymers, polyisobutylene, oleic acid, synthetic rubber based adhesive, vinyl acetate resin base, phosphatidylcholine, propylene glycol, bentonite, butylene glycol, mineral oil and dipropylene glycol.

3. a protective liner of polyester that is attached to the adhesive surface and must be removed before the patch can be used.




The second type of patch contained in ESTALIS-SEQUI and which should be applied to the skin during the last 14 days of a 28-day treatment cycle is ESTALIS 250/50 or ESTALIS 140/50. The active components of the system are estradiol USP and norethindrone acetate USP. The remaining components of the system are pharmacologically inactive; they are: a silicone (BIO PSA® X7-4603) and acrylic (Gelva® 737)-based multipolymeric adhesive, povidone USP, oleic acid NF, and dipropylene glycol.

**Stability And Storage Recommendations**

ESTALIS AND ESTALIS-SEQUI: Store between 2˚C and 8˚C until dispensing. Do not freeze.

After dispensing, the patches may be stored unrefrigerated at 20 to 25˚C, in which case they should be used within 6 months or before the expiry date, whichever comes first. If the patches are stored in the refrigerator, in this case, they should be used before the expiry date and should be allowed to reach room temperature before application to ensure that they stick satisfactorily.

Do not store the patches in areas where extreme temperatures can occur. Each patch is individually sealed in a separate pouch. Do not store out of the pouch. Apply immediately upon removal from the protective pouch. Apply whole patches.

Keep out of the reach and sight of children and pets both before use and when disposing of used patches.

## Availability Of Dosage Forms

The ESTALIS (NETA/estradiol-17ß) package consists of the following systems:

| | ESTALIS 140/ 50 | ESTALIS 250/50 |
|---|---|---|
| Estradiol-17ß Dosage<br>Nominal *in vivo* delivery | 50 µg/day | 50 µg/day |
| NETA Dosage<br>Nominal *in vivo* delivery | 140 µg/day | 250 µg/day |
| Total Estradiol-17ß Content | 0.62 mg | 0.51 mg |
| Total NETA Content | 2.7 mg | 4.8 mg |
| Drug-Releasing Area | 9 $cm^2$ | 16 $cm^2$ |
| Shape of patch | Round | Round |
| Presentation | Cartons of 8 patches | Cartons of 8 patches |

The ESTALIS-SEQUI (estradiol-17ß + NETA/estradiol-17ß) package consists of the following systems:

| | ESTALIS-SEQUI 140/ 50 | | ESTALIS-SEQUI 250/50 | |
|---|---|---|---|---|
| | VIVELLE 50 | ESTALIS 140/ 50 | VIVELLE 50 | ESTALIS 250/50 |
| Estradiol-17ß Dosage Nominal *in vivo* delivery | 50 µg/day | 50 µg/day | 50 µg/day | 50 µg/day |
| NETA Dosage Nominal *in vivo* delivery | -- | 140 µg/day | -- | 250 µg/day |
| Total Estradiol-17ß Content | 4.33 mg | 0.62 mg | 4.33 mg | 0.51 mg |
| Total NETA Content | -- | 2.7 mg | -- | 4.8 mg |
| Drug-Releasing Area | 14.5 $cm^2$ | 9 $cm^2$ | 14.5 $cm^2$ | 16 $cm^2$ |
| Shape of patch | Round | Round | Round | Round |
| Presentation | Cartons of 4 Vivelle and 4 Estalis patches | | Cartons of 4 Vivelle and 4 Estalis patches | |

# INFORMATION FOR THE CONSUMER

Your doctor has prescribed ESTALIS or ESTALIS-SEQUI for you. Please read this "INFORMATION FOR THE CONSUMER' before you start taking ESTALIS or ESTALIS-SEQUI, or if you have your prescription refilled. This information does not take place of talking to your healthcare provider.

**Warning**

As the Women's Health Initiative (WHI) study results indicated increased risk of myocardial infarction (heart attack), stroke, invasive breast cancer, pulmonary emboli (blood clots in the lungs) and deep venous thrombosis (blood clots in the leg veins) in postmenopausal women receiving treatment with combined conjugated equine estrogens and medroxyprogesterone acetate compared to those receiving placebo tablets, the following should be highly considered:

- Estrogen-progestin combinations **should not** be used to prevent heart disease.
- Estrogens with or without progestins should be prescribed at **the lowest effective dose**.
- Estrogens with or without progestins should be used for **the shortest period** possible.

## INTRODUCTION:

## WHAT IS ESTALIS?

**ESTALIS** contains a natural estrogen hormone, estradiol, as well as a progestin, norethindrone acetate (NETA). ESTALIS can alleviate menopausal symptoms and is used continuously throughout the 28-day cycle.

ESTALIS is an alcohol-free, adhesive-based matrix transdermal drug delivery system comprising three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are: a backing, an adhesive layer, and a protective liner. The adhesive matrix containing 17$\beta$-estradiol and norethindrone acetate is applied to a polyester/ethylene vinyl acetate laminate film on one side and is protected on the other side by a transparent fluoropolymer coated release liner. The transparent release liner must be removed before the system can be used. Each patch is enclosed in a heat-sealed pouch.

ESTALIS 140/50 and 250/50 contain a fixed combination of norethindrone acetate (NETA) and estradiol-17ß. ESTALIS patches release controlled amounts of NETA and estradiol-17ß simultaneously through the skin for up to 4 days.

The active components of the system are estradiol USP and norethindrone acetate USP. The remaining components of the system are pharmacologically inactive; they are: a silicone and acrylic -based multipolymeric adhesive, povidone USP, oleic acid NF, and dipropylene glycol.

## WHAT IS ESTALIS SEQUI?

**ESTALIS-SEQUI** contains two types of transdermal therapeutic systems (patches) that are used in sequence (sequential regimen): VIVELLE 50 is used during the first 14 days of your 28-day cycle and ESTALIS 250/50 or ESTALIS 140/50 is used during the last 14 days of your 28-day cycle. VIVELLE contains a natural estrogen hormone, estradiol, while ESTALIS contains estradiol as well as a progestin, norethindrone acetate (NETA). ESTALIS-SEQUI can alleviate menopausal symptoms.

VIVELLE 50 is a thin, circular, multilayer, transparent transdermal therapeutic system, i.e., an adhesive patch, containing estradiol-17ß that is designed for application to an area of intact skin.

The VIVELLE patch comprises three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are a backing film, an adhesive layer and a protective layer:

1. a flexible semi-transparent backing film of polyurethane and ethylene vinyl alcohol polymer.

2. an adhesive formulation containing estradiol-17ß, acrylic polymers, polyisobutylene, oleic acid, synthetic rubber based adhesive, vinyl acetate resin base, phosphatidylcholine, propylene glycol, bentonite, butylene glycol, mineral oil and dipropylene glycol.

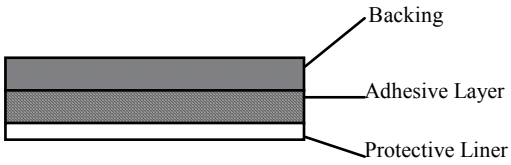
3. a protective silicone coated polyester liner that is attached to the adhesive surface and must be removed before the patch can be used.

The second type of patch contained in ESTALIS-SEQUI and which should be applied to the skin during the last 14 days of a 28-day treatment cycle is ESTALIS 250/50 or ESTALIS 140/50. The active components of the system are estradiol USP and norethindrone acetate USP. The remaining components of the system are pharmacologically inactive; they are: a silicone and acrylic-based multipolymeric adhesive, povidone USP, oleic acid NF, and dipropylene glycol.

ESTALIS and VIVELLE patches are applied twice weekly. Each patch should be worn continuously for 3 to 4 days.

When ESTALIS or VIVELLE are applied to the skin, the patches release small amounts of either estradiol and NETA or estradiol, which passes directly through the skin into your bloodstream. Estradiol is identical to the natural hormone that is produced by your ovaries in large quantities before menopause (the time when your menstrual periods stops).

The use of Hormone Replacement Therapy (HRT) should be done under your doctor's supervision, with a regular follow-up (at least once a year) to identify the adverse events associated with long-term treatment.




This leaflet describes the uses of estrogens and progestins, precautions to take when using these hormones and how to use ESTALIS or ESTALIS-SEQUI. Please read it carefully. **If you want to know more or have any questions, please ask your doctor or pharmacist.**

Decisions regarding hormone replacement therapy and the length of time that a woman takes estrogen must be individualized and are made between each woman and her doctor.

**Uses Of Estrogens**

1. To reduce moderate or severe menopausal symptoms.

Your body normally makes estrogens and progestins (female hormones) mainly in the ovaries. Between ages 45 and 55, the ovaries gradually stop making estrogens. This leads to a decrease in body estrogen levels and a natural menopause (the end of monthly menstrual periods). If both ovaries are removed during an operation before natural menopause takes place, the sudden decrease in estrogen levels causes "surgical menopause".

Menopause is not a disease - it is a natural life event and different women experience menopause and its symptoms differently. Not all women suffer obvious symptoms of estrogen deficiency. When the estrogen levels begin decreasing, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden intense episodes of heat and sweating ("hot flashes" or " hot flushes"). Using estrogen drugs can help the body adjust to lower estrogen levels and reduce these symptoms.

2. To treat vulval and vaginal atrophy

Some women may also develop vulval or vaginal atrophy (itching, burning or dryness in or around the vagina, difficulty or burning on urination) in association with menopause. These changes may be improved by estrogen therapy.

If you have not had a hysterectomy (operation to remove the womb), estrogens should be prescribed in association with a progestin.

**Uses Of Progestins**

Progestins used in hormone replacement therapy have similar effects to the female sex hormone progesterone. During the child bearing years, progesterone is responsible for regulation of the menstrual cycle. The estradiol delivered by ESTALIS or ESTALIS-SEQUI not only relieves your menopausal symptoms, but, like estrogens produced by your body, may also stimulate growth of the inner lining of the uterus, the endometrium. In menopausal and postmenopausal women with an intact uterus, stimulation of growth of the endometrium may result in irregular bleeding. In some cases this may progress into a disorder of the uterus known as endometrial hyperplasia (overgrowth of the lining of the uterus), which increases the risk of endometrial cancer (cancer of the lining of the uterus). The development of estrogen-mediated disorders of the uterus can be reduced if a progestin, such as norethindrone acetate, is given regularly for a certain number of days with your estrogen replacement therapy. For women receiving ESTALIS in a sequential regimen (i.e. ESTALIS-SEQUI), each cycle of progestin administration should induce a periodic bleeding, whereby the inner lining of the uterus is regularly shed, thus protecting against endometrial hyperplasia. For women receiving ESTALIS in a continuous combined regimen, it is expected that uterine bleeding will stop within a period of a few months and such treatment should also be protective of endometrial hyperplasia.

If your uterus has been surgically removed, endometrial hyperplasia cannot occur and cyclical administration of a progestin is not necessary (except if your uterus has been removed and you have residual endometriosis).

You and your doctor should discuss the benefits and risks of ESTALIS and ESTALIS-SEQUI and other alternative therapies.

## RESTRICTIONS ON USE:

## WHO SHOULD NOT TAKE ESTALIS OR ESTALIS SEQUI

Certain medical conditions may be aggravated by estrogens and progestins, therefore these hormones should either not be used at all or should be used with precaution under these conditions.

**ESTALIS OR ESTALIS-SEQUI should not be used under the following conditions:**

- if you are pregnant or think you may be pregnant. Since pregnancy may be possible early in menopause while you are still having spontaneous periods, the use of non-hormonal birth control should be discussed with your physician at this time. If you take estrogen during pregnancy, there is a small risk of your unborn child having birth defects.

- if you are breast-feeding. Ask your doctor or pharmacist for advice.
- if you currently have or have ever had cancer of the breast or endometrium (lining of the womb) or any other estrogen-dependent cancer
- If you have been diagnosed with endometrial hyperplasia (overgrowth of the lining of the uterus)
- if you have unexpected or unusual vaginal bleeding
- if you have active phlebitis (inflamed varicose veins)
- if you currently have a problem with blood clots forming in your blood vessels or have ever had such a problem in the past. This may cause painful inflammation of the veins (thrombophlebitis) or blockage of a blood vessel in the legs (deep vein thrombosis), lungs (pulmonary embolism) or other organs
- if you have ever had a heart attack or stroke
- if you have serious liver disease
- if you have migraine or severe headaches
- if you have had partial or complete loss of vision due to blood vessel disease in the eye.
- if you have a disease of blood pigment called porphyria
- if you have had any unusual allergic reaction to estrogens or any other component of ESTALIS or ESTALIS-SEQUI (see Pharmaceutical Information).

ESTALIS and ESTALIS-SEQUI are not contraceptives, nor will they restore fertility.

Talk to your doctor if you have any further questions or if you think that any of the above may apply to you.

## ESTALIS & ESTALIS SEQUI and Children

ESTALIS and ESTALIS SEQUI should not be used in children

## WARNINGS AND PRECAUTIONS

Although estrogens and progestins provide health benefits, certain precautions should be taken before their use and in some situations their use may not be appropriate. See your doctor regularly and at least once a year for check-ups. Some women will need to go more often. You should discuss with your doctor the need for adjusting or continuing therapy.

### Endometrial carcinoma

The use of estrogens has been reported to increase the risk of cancer of the lining of the uterus (endometrial cancer) in women after the menopause. **This risk is significantly reduced when estrogen is used along with a progestin.** If you have had your uterus removed by a hysterectomy, uterine cancer would not be a risk for you and cyclical administration of a progestin is not necessary. Therefore, ESTALIS and ESTALIS-SEQUI should not be used in this situation.

## Endometrial hyperplasia

If your uterus has not been removed, estrogen therapy can increase the risk of endometrial hyperplasia (overgrowth of the lining of the uterus). It has been shown that adequate addition of progestin therapy to estrogen therapy, as with ESTALIS or ESTALIS-SEQUI, lowers the incidence of endometrial hyperplasia (see **Use of Progestins)**.

## Breast cancer

Women with a family history of breast cancer, or with breast nodules, fibrocystic breast disease (lumps), or abnormal mammograms should consult with their doctor before starting hormone replacement therapy. Your doctor will check your breasts and your pelvis. Regular breast examinations by a health professional and monthly self-examination are recommended for all women. This helps to monitor for unwanted effects of HRT. Tell your doctor if you suspect any abnormality. The overall benefits and possible risks of hormone replacement therapy should be discussed with the physician.

## Venous thromboembolism

A recent study indicated that the use of estrogen with or without progestin is associated with an increased risk of developing venous thromboembolism (blood clots in the veins). Make sure you tell your doctor if you think you may be at increased risk of thrombosis (formation of blood clots in your blood vessels). The risk increases with age and may also be increased if:

- if you or anyone in your immediate family has ever had thrombosis blood clots in the blood vessels of the legs or the lungs
- if you have varicose veins
- if you have systemic lupus erythematosus (a connective tissue disease)
- if you are overweight
- If you smoke

Tell your doctor well in advance of any expected hospitalization or surgery. If you have to go into hospital unexpectedly, tell the doctor who admits you that you are using ESTALIS or ESTALIS-SEQUI. The risk of developing blood clots in your blood vessels may be temporarily increased as a result of an operation, serious injuries or having to stay in bed for a prolonged period. ESTALIS and ESTALIS-SEQUI should not be restarted until you are fully mobile.

## Stroke and cardiac disease

A recent study indicated that the use of estrogen with or without progestin is associated with an increased risk of stroke and coronary heart disease. Before starting an estrogen therapy, you should discuss the benefits and risks with your doctor.

## Gallbladder disease

The use of oral estrogens after menopause has been reported to increase the risk of gallbladder disease requiring surgery.

## Dementia

Recent studies indicate that the use of combined estrogen and progestin in women age 65 and older may increase the risk of developing probable dementia (decline of memory or mental ability).

Ask your doctor or pharmacist to answer any questions you may have.

**Take special care with ESTALIS and ESTALIS-SEQUI**

Before you start using ESTALIS or ESTALIS-SEQUI, you will discuss with your doctor your personal medical history and that of your family. You will also be given a complete physical and gynecological examination. You may be advised to have a mammogram prior to the start of your treatment and at regular intervals during treatment, as deemed appropriate by your doctor. To help your doctor decide whether you should use ESTALIS or ESTALIS-SEQUI and what precautions should be taken during use, tell your doctor:

- what other prescription and nonprescription medicines, if any, you are taking. There are some medicines which interfere with the effects of estrogens.
- about any allergies or sensitivities to medicines or any other substances you may have.
- if you are undergoing surgery or need long bed rest
- if you have ever had any of the following:
  - ⇨ high blood pressure
  - ⇨ phlebitis (inflamed varicose veins)
  - ⇨ abnormal blood clotting
  - ⇨ heart, kidney, or liver problems
  - ⇨ gallbladder disease
  - ⇨ porphyria
  - ⇨ systemic lupus erythematosus
  - ⇨ asthma

- ⇨ diabetes
- ⇨ abnormalities of the breast (such as lumps) or uterus
- ⇨ endometriosis (disorder of the pelvis causing painful menstrual periods)
- ⇨ uterine fibroids or other benign tumors of the womb
- ⇨ breast cancer in your immediate family
- ⇨ breast disease, breast biopsies
- ⇨ epilepsy or other neurological disorders
- ⇨ migraine
- ⇨ depression
- ⇨ otosclerosis (hearing loss due to a problem with the bones in the ear)
- ⇨ high levels of lipids in your blood
- ⇨ jaundice or itching related to estrogen use or during pregnancy

Your doctor may want to take special precautions if you have any of these conditions.

**How long to use ESTALIS or ESTALIS-SEQUI**

ESTALIS and ESTALIS-SEQUI should be used only as long as needed.

Periodically (at least yearly), you should discuss with your doctor the possible risks and benefits associated with HRT and whether you still need the treatment.

Women who use HRT may have an increased risk of developing blood clots, breast cancer, cancer of the uterus (womb), heart disease and stroke, or probable dementia (decline of memory or mental ability).

Women taking estrogens alone for a long time may have a higher risk of developing ovarian cancer than women not using estrogens. The risk with ESTALIS or ESTALIS-SEQUI treatment, which combines estrogens and progestogens, is not known.

You and your doctor should discuss these risks and benefits, taking into account your personal medical status.

## ADVERSE EFFECTS

All medicines can have side effects. Sometimes they are serious, most of the time they are not.

**Tell your doctor immediately and remove the patch if any of the following occurs:**

- signs of an allergic reaction: sudden troubled breathing, tightness of the chest, general rash, swelling or itching
- signs of jaundice: yellowing of the eye or skin
- signs that blood clots may have formed in your body: pain or heaviness in the calves, legs, thighs or chest, sudden shortness of breath, coughing blood or dizziness
- tender or painful inflammation of the veins
- signs of heart attack: chest pain, dizziness, nausea, shortness of breath, irregular pulse
- signs of stroke: collapse, numbness or weakness of the arms and the legs, headache, dizziness and confusion, visual disturbance, difficulty swallowing, slurred speech and loss of speech

The above side effects are serious and require urgent medical attention. These side effects are rare.

**Check with your doctor as soon as possible if any of the following occur:**

- swelling of the lower legs, ankles, fingers or abdomen due to fluid retention
- fluid retention persisting for more than 6 weeks
- change in weight
- change in your sex drive
- easy bruising, excessive nose bleeds, excessive heavy periods (may be signs of abnormal blood clotting)
- irregular vaginal bleeding or constant spotting (signs of endometrial hyperplasia)
- lower abdominal pain or swelling, painful and/or heavy periods (may be signs of growth of fibroids in the uterus)
- back pain or menstrual period-like pain
- change in vaginal discharge (may be sign that too much estrogen is taken)
- vaginal thrush (vaginal fungal infection with severe itching, vaginal discharge)
- itching, inflammation or fluid discharge of the vagina
- intolerable breast tenderness

- breast tenderness and excessive vaginal secretions (may be sign that too much estrogen is taken)
- breast enlargement or lumps
- increase in blood pressure
- persistent or severe skin irritation
- spotty darkening of the skin, particularly on the face (chloasma)
- rash, itching, acne, dryness or discoloration of the skin
- itching under the patch, reddening of the skin after the patch has been removed; hair loss, excessive hairiness.
- Depression, headache, migraine, decline of memory or mental ability, dizziness, uncontrollable jerky movements (chorea)
- Nervousness, rapid change in mood, difficulty sleeping
- changes in vision
- contact lens discomfort
- hearing loss
- nausea, bloating of the stomach, abdominal pain, diarrhea, indigestion, vomiting, tender abdomen (may be signs of gallbladder disease)
- gallstones, gallbladder disease
- upper abdominal pain or swelling (may be signs of liver tumors)

Progestins may produce side effects such as breast tenderness, mood swings and weight changes.

In addition, ESTALIS or ESTALIS-SEQUI may produce some redness or irritation under or around the patch in some women (**see Helpful Hints**).

**Tell your doctor if you notice any unusual symptoms or any other side adverse effects not mentioned in this leaflet.**

## HOW TO USE ESTALIS

ESTALIS packs contain 8 patches. ESTALIS (NETA/17β-estradiol) patches are available in two strengths , called ESTALIS 140/50 and ESTALIS 250/50, each containing and releasing different amounts of estradiol and norethindrone acetate, as follows:

- ESTALIS 140/50: 9 $cm^2$ patch, containing 0.620 mg estradiol and 2.70 mg NETA, and releasing about 50 µg estradiol and 140 µg NETA per day.
- ESTALIS 250/50: 16 $cm^2$ patch, containing 0.512 mg estradiol and 4.80 mg NETA, and releasing about 50 µg estradiol and 250 µg NETA per day.

When ESTALIS is applied to the skin, the patch releases small amounts of estradiol and NETA, which pass directly through the skin into your bloodstream. Your doctor will prescribe the patches in a continuous regimen.

*Continuous Regimen*

The ESTALIS patch is worn continuously for the 4 weeks of the cycle (see Figure 1). The ESTALIS patches are applied twice weekly on the same days of each week. Each patch should be worn continuously for 3-4 days.

Figure 1

| | | | |
|---|---|---|---|
| Week 1 | ◯ | ◯ | ESTALIS patch for the 4 weeks of the cycle |
| Week 2 | ◯ | ◯ | |
| Week 3 | ◯ | ◯ | |
| Week 4 | ◯ | ◯ | |

The next treatment cycle is started immediately after removal of the last ESTALIS patch. Irregular uterine bleeding may occur particularly in the first 6 months, but generally decreases with time.

It is important that you take your medication as your physician has prescribed. Do not discontinue or change your therapy without consulting your physician first.

## HOW TO USE ESTALIS-SEQUI

Each ESTALIS-SEQUI pack contains four VIVELLE and four ESTALIS patches (see above). The VIVELLE patch provides the estrogen, estradiol, as follows:

- Vivelle 50: 14.5 $cm^2$ patch, containing 4.33 mg estradiol and releasing about 50 µg estradiol per day.

The ESTALIS patch provides estradiol and the progestin, norethindrone acetate (NETA). **All eight patches are to be used in a 28-day treatment cycle.**

Sequential Regimen:

Therapy is started with the VIVELLE only patches which are used for the first 2 weeks followed by the ESTALIS patches for the next 2 weeks (See Figure 2). The VIVELLE and ESTALIS patches are applied twice weekly on the same days of each week. Each patch should be worn continuously for 3-4 days.

Figure 2

<table>
<tr><td>Week 1</td><td>  </td><td>  </td><td rowspan="2">VIVELLE patch for the first 2 weeks</td></tr>
<tr><td>Week 2</td><td>  </td><td>  </td></tr>
<tr><td>Week 3</td><td>  </td><td>  </td><td rowspan="2">ESTALIS patch for the following 2 weeks</td></tr>
<tr><td>Week 4</td><td>  </td><td>  </td></tr>
</table>

Regular uterine cyclical bleeding usually starts towards the end of the ESTALIS application phase (i.e., while you are wearing the 4th ESTALIS patch of that cycle). The duration of bleeding is around 6 days. Bleeding is of light intensity or spotting for 60-70% of this time.

The next treatment cycle is started with the VIVELLE patch immediately after removal of the last ESTALIS patch, and regardless of whether there is still uterine bleeding (i.e., you will have a patch on at all times).

It is important that you take your medication as your physician has prescribed. Do not discontinue or change your therapy without consulting your physician first.

## Taking other medicines with ESTALIS or ESTALIS-SEQUI

**Tell your doctor or pharmacist if you are taking or have recently taken any other medicines. Remember also those not prescribed by a doctor.**

This particularly includes the following: anti-anxiety medicines (meprobamate), anti-epileptic medicines (e.g. barbiturates, phenytoin or carbamazepine), an anti-inflammatory medicine called phenylbutazone, antibiotics and other anti-infective medicines (e.g. rifampicin, rifabutin, nevirapine, efavirenz, ritonavir, nelfinavir), and herbal medicines (e.g. St John's wort).

These medicines may be affected by ESTALIS or ESTALIS-SEQUI or, conversely, they may affect how well ESTALIS or ESTALIS-SEQUI work. Your doctor may need to adjust the dose of your treatment.

### How ESTALIS and ESTALIS-SEQUI Work

Treatment with ESTALIS and ESTALIS-SEQUI offer relief from menopausal symptoms for women with a uterus. With ESTALIS-SEQUI-(sequential regimen), you receive estradiol throughout the entire 28-day cycle, and norethindrone acetate (NETA), a progestin, during the last 2 weeks of the 28-day cycle. With ESTALIS used in a continuous regimen, you receive estradiol and norethindrone acetate (NETA), a progestin, throughout the entire 28-day cycle. The progestin provides important protection for your uterus **(See Uses Of Progestins)**.

The main estrogen produced by your ovaries prior to menopause is estradiol, and this is the same estrogen that is in ESTALIS and ESTALIS-SEQUI. When applied to the skin, the ESTALIS and ESTALIS-SEQUI patches continually releases small, controlled quantities of estradiol, which pass through your skin and into your bloodstream. The amount of estrogen prescribed depends on your body's needs.

By providing estradiol, ESTALIS and ESTALIS-SEQUI offer relief from menopausal symptoms.

### How And Where To Apply ESTALIS and ESTALIS-SEQUI

It is recommended that you change the site of application each time the patch is applied. In other words, each time you apply a patch, place it on a different area of your abdomen or buttocks than used before. The same area should not be used again for at least one week. However, each time you apply a patch you should always apply it to the same area of your body (i.e., if the patch is applied

to the buttocks, move the patch from right side to left side, twice a week or more if there is any redness under the patch).

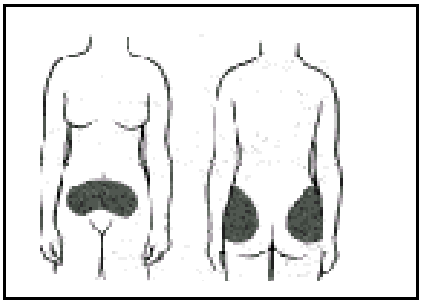
**1. Preparing The Skin**

In order for the patch to stick, the skin should be clean, dry and free of creams, lotions or oils. If you wish, you may use body lotion after the patch has been properly applied to the skin. The skin should not be irritated or broken, since this may alter the amount of hormone you get. Contact with water (bath, pool, or shower) should not affect the patch **(see Helpful Hints)**.

**2. Where To Apply The ESTALIS Or ESTALIS-SEQUI Patches**

The patches may be applied to the buttocks or abdomen (see Figure 3). Change the site of application each time you put a patch on. A **one week period** should elapse before applying the patch to a previously used spot.

Figure 3



Avoid areas of the skin where clothing may rub the patch off or areas where the skin is very hairy or folded. Also avoid areas where the patch is likely to be exposed to the sun since this may affect how the patch works.

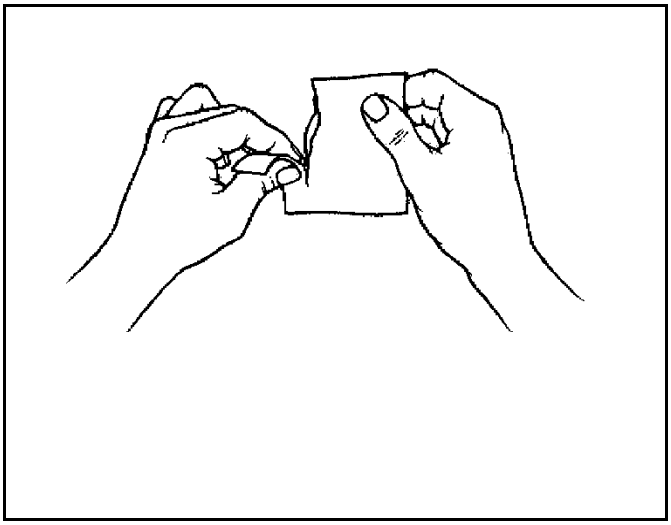
**DO NOT APPLY THE PATCHES TO YOUR BREAST**, since this may cause unwanted effects and discomfort.

**3. Opening The Pouch**

The patches contained in ESTALIS and those contained in ESTALIS-SEQUI (i.e. VIVELLE and ESTALIS) are individually sealed in a protective pouch. **Tear** open this pouch at the indented notch

and remove the patch (see Figure 4). Do not use scissors, as you may accidentally cut and destroy the patch.

Figure 4

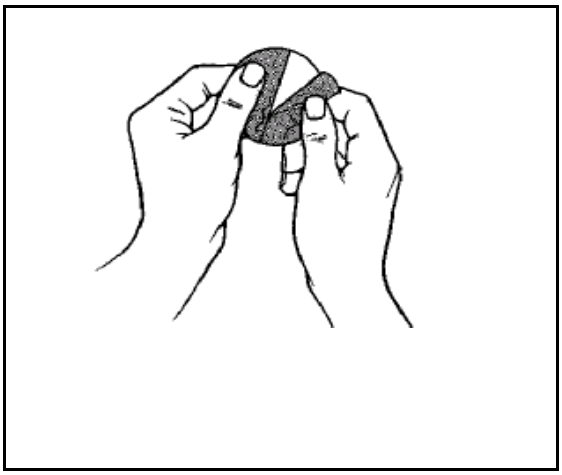


**4. Removing The Liner**

One side of the patch has the adhesive that sticks to your skin. The adhesive is covered by a protective liner that must be removed.

To separate the patch from the liner, hold the patch with the protective liner facing you. Peel off one half of the protective liner and discard it (see Figure 5). Try to avoid touching the sticky side of the patch with your fingers.

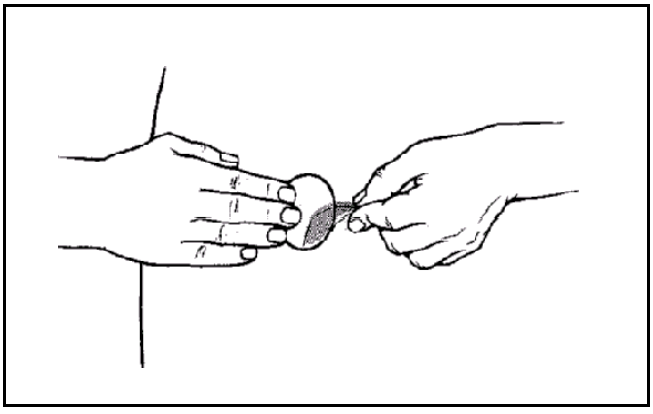
Figure 5



Using the other half of the liner as a handle, apply the sticky side of the system to a dry area of intact skin on your abdomen or buttocks. Press the sticky side on the skin and smooth down.

Fold back the remaining side of the edge of the protective liner and pull it across the skin (see Figure 6). Avoid touching the adhesive.

Figure 6



**5. Applying The ESTALIS and ESTALIS-SEQUI patches**

Apply the adhesive side to the spot you have chosen. Press it firmly in place with the palm of your hand for about 10 seconds, then run your finger around the edge, making sure there is good contact with the skin. Apply the patch soon after opening the pouch and removing the liner.

**6. When And How To Remove The Patch**

Continuous Regimen: The ESTALIS patch should be changed twice weekly. Always change it on the same 2 days of the week. If you forget to change it at the scheduled time, there is no cause for alarm. Just change it as soon as possible and **continue** to follow your usual schedule.

Sequential-Regimen: The VIVELLE patches used during weeks 1 and 2 should be changed twice weekly. The ESTALIS patches used during weeks 3 and 4 should also be changed twice weekly. Always change the patch on the same 2 days of the week. If you forget to change it at the scheduled time, there is no cause for alarm. Just change it as soon as possible and **continue** to follow your usual schedule.

After you remove the patch fold it in half with the adhesive sides inwards. **Throw it away, safely out of the reach of children or pets**.

Any adhesive left on your skin should rub off easily. You can also use mineral oil, baby oil or rubbing alcohol to remove adhesive from the skin. Apply a new ESTALIS or ESTALIS-SEQUI patch on a different spot of clean, dry skin.

**7. If you forget to use ESTALIS or ESTALIS-SEQUI**

If you miss applying a patch, apply a new patch as soon as you remember. No matter what day that happens, go back to changing this patch on the same day as your initial schedule.

**Helpful Hints**

**What to do if the patch falls off**

Should a patch fall off in a very hot bath or shower, shake the water off the patch. Dry your skin completely and reapply the patch as soon as possible (to a different area of skin) and continue your regular schedule. Make sure you choose a clean, dry, lotion-free area of skin. If it still does not stick completely to your skin, then use a **new** patch. No matter what day this happens, go back to changing the patch on the same days as the initial schedule.

If hot baths, saunas or whirlpools are something you enjoy and you find that the patch is falling off, you may consider removing the patch **temporarily** while you are in the water. If you do remove the patch temporarily, the adhesive side of the patch should be placed on the protective liner that was removed when originally applying the patch. Wax paper may be used as an alternate to the liner. This prevents the contents of the patch from emptying by evaporation while you are not wearing it.

In addition to exposure to very hot water, there are some other causes for the patch failing to stick. If you are having patches fall off regularly, this could be happening as a result of:

- using any type of bath oil
- using soaps with a high cream content
- using skin moisturizers before applying the patch

Patch adhesion may be improved if you avoid using these products, and by cleansing the site of application with rubbing alcohol before you apply the patch.

**What to do if your skin becomes red or irritated under or around the patch**

As with any product that covers the skin for a period of time (such as bandages), the ESTALIS patches can produce some skin irritation in some women. This varies according to the sensitivity of each woman.

Usually this redness does not pose any health concern to you, but to reduce this problem, you may change the site of application of the ESTALIS or ESTALIS-SEQUI patches every time a new patch is applied.

Experience with another patch, VIVELLE, has shown that if you allow the patch to be exposed to the air for approximately 10 seconds after the protective liner has been removed, skin redness may not occur.

If redness and/or itching continues, you should consult your physician.

**Always Remember**

Your doctor has prescribed ESTALIS or ESTALIS-SEQUI for you after a careful review of your medical needs. Use it only as directed and do not give it to anyone else. Your doctor should re-examine you at least once a year.

If you have any questions, contact your doctor or pharmacist.

## SYMPTOMS AND TREATMENT OF OVERDOSAGE

**Symptoms**

Overdosage with estrogen may cause nausea, breast discomfort, fluid retention, bloating or vaginal bleeding in women.

Progestin (norethindrone acetate) overdosage has been characterized by depressed mood, tiredness, acne and hirsutism.

**Treatment**

Owing to the mode of administration (transdermal), plasma levels of estradiol-17ß and norethindrone acetate can be rapidly reduced by removal of the patch.

## PHARMACEUTICAL INFORMATION

**ESTALIS**: Like most medicines, ESTALIS contains other substances in addition to estrogen and a progestin. The other substances are silicone and acrylic-based multipolymeric adhesive, povidone USP, oleic acid NF, and dipropylene glycol.

**ESTALIS-SEQUI:** In addition to the ESTALIS patches described above, ESTALIS-SEQUI contain VIVELLE patches. Like most medicines, VIVELLE contains other substances in addition to estrogen. The other substances are acrylic copolymers, bentonite, butylene, dipropylene and propylene glycols, ethylene-vinyl alcohol copolymer, mineral oil, oleic acid, phosphatidylcholine, polyester, polyisobutylene, polyurethane and synthetic rubber, vinyl acetate resin.

**STORAGE**

ESTALIS and ESTALIS-SEQUI patches can be stored at room temperature (20- 25°C). In this case, use the patches within 6 months of purchase or before the expiry date shown on the pack, whichever comes first. You may also store the patches in a refrigerator (2-8°C), in which case you should use the patches before the expiry date shown on the pack and allow them to reach room temperature before you apply them.

Do not freeze. **Store in the original package.** Apply whole patches.

ESTALIS and ESTALIS-SEQUI patches should be kept out of the reach and sight of children and pets before and after use.

Use ESTALIS and ESTALIS-SQUI within 6 months of purchase or before the expiry date shown on the pack, whichever comes first.

Do not use any ESTALIS or ESTALIS-SEQUI pack that is damaged or shows signs of tampering.

# PHARMACOLOGY

## Primary Pharmacologic Activity

### Estradiol-17ß

Estradiol-17ß is the major estrogenic hormone secreted by the human ovary. Among numerous effects, estradiol-17ß is largely responsible for the development and maintenance of the female reproductive system and of secondary sexual characteristics. It promotes growth and development of the vagina, uterus, fallopian tubes, and breasts. Estradiol-17ß contributes to the shaping of the skeleton, to the maintenance of tone and elasticity of urogenital structures, to changes in the epiphyses of the long bones that allow for the pubertal growth spurt and its termination, to the growth of axillary and pubic hair, and to the pigmentation of the nipples and genitals. Estradiol-17ß also affects the release of pituitary gonadotropins.

After menopause, when the ovaries have ceased to function, only small amounts of estradiol-17ß are still produced, i.e., from the aromatization of androstenedione to estrone and to a lesser extent, testosterone to estradiol-17ß. Estrone is transformed to estradiol-17ß by the enzyme 17ß-hydroxysteroid-dehydrogenase. Both enzymes prevail in fat, liver and muscle tissue.

In premenopausal women, the ratio of estradiol-17ß ($E_2$) to estrone ($E_1$) (i.e., $E_2/E_1$ ratio) in the plasma is in the range of 0.5 to 2, depending on the phase of the menstrual cycle. The $E_2/E_1$ ratio for untreated postmenopausal women is below 0.5.

Loss of the ovarian estradiol-17ß production after menopause can result in the following: instability of thermoregulation causing hot flushes associated with sleep disturbance and excessive sweating; accelerated loss of bone matrix and mineral, resulting in osteoporosis; alterations in lipid metabolism; urogenital atrophy, causing dyspareunia and urinary incontinence.

### Norethindrone Acetate

Norethindrone acetate (NETA) is a potent progestin that essentially mimics the biological effects of progesterone. Tissue effects of NETA are dependent on prior estrogen stimulation, and NETA receptors have been identified in all tissues containing estrogen receptors **(see Estradiol-17ß above)**.

NETA induces protein synthesis and also reduces the number of estrogen and progestin receptors, thereby limiting excessive growth stimulation of target tissues by estrogen. 17-hydroxysteroid-dehydrogenase, which locally oxidizes estradiol-17ß to its weaker estrogenic metabolite estrone, is also induced by NETA.

One of the major targets of NETA is the uterus, where it induces secretory transformation of the estrogen-primed endometrium. Once transformation of the endometrium is completed, the estrogen-primed endometrium is shed resulting in a regular cyclical bleeding.

**Hormone Replacement Therapy**

ESTALIS (NETA/estradiol-17ß) provides continuous, controlled transdermal delivery of estradiol-17ß such that estradiol-17ß levels as well as the $E_2/E_1$ ratio in postmenopausal women are restored to those seen in the early follicular phase of the premenopausal range **(see Pharmacokinetics And Metabolism)**. ESTALIS thus alleviates the symptoms of estradiol-17ß deficiency in postmenopausal women.

**Coadministration Of Progestins**

Estrogen replacement therapy should be supplemented by sequential progestin therapy only in women with an intact uterus.

It is not possible to give accurate values for the relative clinical effectiveness of different progestins because careful comparisons are limited in number, and different responses have been used in the published studies. In various tests in women, the relative potencies of the progestins are not the same. Furthermore, some progestins possess more or less estrogenic and androgenic activities than do others.

In general, progestins have been administered sequentially for 10 to 14 days during each estrogen cycle. Published data suggest that 12 to 14 days of sequential progestin treatment during estrogen replacement therapy virtually eliminates the occurrence of endometrial hyperplasia, and thereby irregular bleeding and endometrial carcinoma, compared to estrogen treatment alone. The progestin requirements may vary amongst patients.

**Pharmacokinetics And Metabolism**

**Estradiol-17ß**

Metabolism and plasma levels of estradiol-17ß delivered transdermally are similar to those in premenopausal women.

Administration of ESTALIS every 3 to 4 days in postmenopausal women produces average steady-state estradiol serum concentrations of 45 to 50 pg/mL, which are equivalent to the normal ranges observed at early follicular phase in premenopausal women. These concentrations are achieved within 12 to 24 hours following ESTALIS application and are sustained for the entire patch wear period. Minimal fluctuations in serum estradiol concentrations are observed following ESTALIS application, indicating consistent hormone delivery over the application interval. Additionally, transdermal administration of estradiol is reported to produce mean serum concentrations of estradiol comparable to those produced by daily oral administration (oral dose about 20 times the daily transdermal dose).

Transdermally delivered estradiol is metabolized only to a small extent by the skin and by-passes the first-pass effect seen with orally administered estrogen products. Therapeutic estradiol serum levels with lower circulating levels of estrone and estrone conjugates are achieved with smaller transdermal doses (daily and total) as compared to oral therapy, and more closely approximate premenopausal concentrations.

Estradiol has a short elimination half-life of approximately 2 to 3 hours. Therefore, a rapid decline in serum levels is observed after the ESTALIS system is removed. Within 4 to 8 hours following ESTALIS removal, serum estradiol concentrations return to untreated, postmenopausal levels (<20 pg/mL).

Concentration data from Phase II and III studies indicate that the pharmacokinetics of estradiol did not change over time, suggesting no evidence of the accumulation of estradiol following extended patch wear period (up to 1 year).

**Norethindrone Acetate**

Progestins used in therapy are well-absorbed through the skin, mucous membranes, and gastrointestinal tract.

Norethindrone steady concentrations are attained within 24 hours of application of the ESTALIS transdermal delivery systems. Minimal fluctuations in serum norethindrone concentrations are observed following ESTALIS treatment, indicating consistent hormone delivery over the application interval. Steady-state norethindrone concentrations are maintained throughout the application interval and are within a therapeutic range sufficient to prevent endometrial hyperstimulation. Serum concentrations of norethindrone increase linearly with increasing doses of norethindrone acetate.

In plasma, norethindrone is bound approximately 90% to SHBG and albumin.

Norethindrone acetate is hydrolyzed to the active moiety, norethindrone, in most tissues including skin and blood. Norethindrone is primarily metabolized in the liver, however, transdermal administration significantly decreases metabolism because hepatic first-pass uptake is avoided.

The elimination half-life of norethindrone is reported to be 6 to 8 hours. Norethindrone serum concentrations diminish rapidly and are less than <50 pg/mL within 48 hours after removal of the ESTALIS transdermal delivery system.

Concentration data from Phase II and III studies indicate that the pharmacokinetics of norethindrone did not change over time, suggesting no evidence of the accumulation of norethindrone following extended patch wear period (up to 1 year).

## TOXICOLOGY

There was no significant dermal irritation seen with ESTALIS. The effects observed in dermal toxicity studies in rats are expected effects of estradiol and norethindrone acetate in rodents. ESTALIS was negative in a contact sensitization study in guinea pigs, a phototoxicity study in rabbits, and a photoallergy study in guinea pigs.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. Long-term continuous administration of natural and synthetic progestins increases the frequency of benign liver tumors in male mice, but not in male or female rats.

Norethindrone acetate was not mutagenic in a battery of *in vitro* or *in vivo* genetic toxicity assays.

**Selected Bibliography**

ARMSTRONG BK.
Oestrogen therapy after menopause-boon or bane?
Med J Aust 1988;148:213-214

BALFOUR J, HEEL R
Transdermal Estradiol: A Review of its Pharmacodynamic and Pharmacokinetic Properties and Therapeutic Efficacy in the Treatment of Menopausal Complaints.
Drugs, 1990; 40: 561-582

BARRET-CONNOR E
Risks and Benefits of Replacement Estrogen.
Annu Rev Med, 1992; 43: 240-242

BERGKVIST L, et al.
The risk of breast cancer after estrogen and estrogen-progestin replacement.
N Engl J Med 1989; 321 (5): 293-297

BRINTON LA, HOOVER RN, FRAUMENI JF Jr.
Menopausal estrogens and breast cancer risk: an expanded case-control study.
Br J Cancer 1986;54:825-832

CAMPOS H, McNAMARA J, WILSON P *et al.*
Differences in Low Density Lipoprotein Subfractions and Apolipoproteins in Premenopausal and Postmenopausal Women.
J Clin Endocrinol Metab, 1988; 67: 30-35

CHEANG A, SITRUK-WARE R, UTIAN W
A Risk-Benefit Appraisal of Transdermal Estradiol Therapy.
Drug Safety, 1993; 9: 367-379

CHETKOWSKI RJ, et al.
Biologic effects of transdermal estradiol.
N Engl J Med 1986; 314 (25): 1615-1620

CHLEBOWSKI RT, HENDRIX SL, LANGER RD, et al. The Women's Health Initiative randomized trial. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women. JAMA. 2003; 289 (24):3243-3253.

CLISHAM P, et al.

Bleeding patterns and endometrial histology (EH) with long-term transdermal estrogen therapy (TE).
Fertil and Steril 1988; Suppl.: 24f

COLDITZ GA, et al.
Prospective study of estrogen replacement therapy and risk of breast cancer in postmenopausal women.
JAMA 1990; 264 (20): 2648-2653

COLDITZ GA, et al.
The use of estrogens and progestins and the risk of breast cancer in postmenopausal women.
N Engl J Med 1995; 332 (24): 1589-1593

COLDITZ GA, EGAN KM, STAMPFER MJ.
Hormone replacement therapy and risk of breast cancer: Results from epidemiologic studies.
Am J Obstet Gynecol 1993;168:1473-1480

COLLABORATIVE GROUP on hormonal factors in breast cancer.
Breast Cancer and Hormone Replacement Therapy.
The Lancet 1997;350:1047-1059

CROOK D, et al.
Comparison of transdermal and oral estrogen-progestin therapy: Effects of serum lipids and lipoproteins.
Am J Obstet Gynecol 1992; 116: 950-955

CUST MP, GANGAR KF, HILLARD TC *et al*.
A Risk-Benefit Assessment of Estrogen Therapy in Postmenopausal Women.
Drug Safety, 1990; 5: 345-358

DALY E, VESSEY MP, et al.
Risk of Venous thromboembolism in users of hormone replacement therapy.
Lancet 1996; 348: 977-80

DALY E, VESSEY MP, PAINTER R.
Case-control study of venous thromboembolism risk in users of hormone replacement therapy.
Lancet 1996:348: 1027-1030

DAVIS GF, and WINTER L.
Cumulative irritation study of placebo transdermal estrogen patches.
Curr Ther Res 1987; 42: 721-719

DUPONT WD, PAGE DL.
Menopausal estrogen replacement therapy and breast cancer.
Arch Intern Med 1991;151:67-72

Editorial
Transdermal estrogen.
Med Lett Drugs Ther 1985; 27 (699): 119-120

GRAMBELL RD.
Update on hormone replacement therapy.
Am Fam Phys 1992;46:87-96S

GAMBRELL RD.
Evidence supports estrogen-progestogen replacement therapy.
Postgrad Med 1985; 78 (1): 35-38

GAMBRELL RD.
Hormones in the etiology and prevention of breast and endometrial cancer.
South Med J 1984; 77 (12): 1509-1515

GRADY S, HERRINGTON D, BITTNER V, et al for the HERS Research Group.
Cardiovascular disease outcomes during 6.8 years of hormone therapy. Heart and Estrogen/progestin replacement study follow-up (HERS II). JAMA. 2002; 288(1):49-57

GRODSTEIN F, STAMPFER MJ, et al.
Prospective study of exogenous hormones and risk of pulmonary embolism in women.
Lancet 1996; 348: 983-987

HULLEY S, GRADY D, BUSH T, et al for the Heart and Estrogen/progestin
Replacement Study (HERS) Research Group. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA 1998; 280(7):605-613

HUNT K, VESSEY M, McPHERSON K.
Long term surveillance of mortality and cancer incidence in women receiving hormone replacement therapy.
Obstet Gynaecol 1987;94:620-635

KAUFMAN DW, MILLER DR, ROSENBERG L, et al.
Non-contraceptive estrogen use and the risk of breast cancer.
JAMA 1984;252:63-67

JICK H, DERBY LE, et al.

Risk of hospital admission for idiopathic venous thromboembolism among users of postmenopausal oestrogens.
Lancet 1996; 348: 981-983

LA VECCHIA C, et al.
Non-contraceptive oestrogens and the risks of breast cancer in women.
Int J Cancer 1986; 38: 853-858

LAUFER LR, et al.
Estrogen replacement therapy by transdermal estradiol administration.
Am J Obstet Gynecol 1983; 146 (5): 533-540

MATTHEWS K, MEILAHN E, KULLER L *et al*.
Menopause and Risk Factors for Coronary Heart Disease.
N Engl J Med, 1989; 321: 641-646

PADWICK ML, et al.
A simple method for determining the optimal dosage of progestogen in postmenopausal women receiving estrogens.
N Engl J Med 1986; 315 (15): 930-934

PALMER JR, ROSENBERG L, CLARKE EA, et al.
Breast cancer risk after estrogen replacement therapy: Results from the Toronto breast cancer study.
Am J Epidemiol 1991;134:1386-1395

PEREZ GUTTHANN S, GARCIA RODRIGUES LA, et al.
Hormone replacement therapy and risk of venous thromboembolism: population based case-control study.
Br Med J 1997; 314: 796-800

POWERS MS, et al.
Pharmacokinetics and pharmacodynamics of transdermal dosage forms of 17ß-estradiol: Comparison with conventional oral estrogens used for hormone replacement.
Am J Obstet Gynecol 1985; 152 (8): 1099-1106

SCHAIRER C, LUBIN J, TROISI R, et al.
Menopausal Estrogen and Estrogen-Progestin Replacement Therapy and Breast Cancer Risk,
JAMA 2000: 283 (4): 485-491.

SHUMAKER SA, LEGAULT, C, RAPP SR, et al. The Women's Health Initiative

Memory Study: A randomised controlled trial. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women.
JAMA. 2003; 289 (20): 2651-2662.

SILLERO-AREMAS M, DELGADO-RODRIGUEZ M. RODRIGUES-CANTERAS R, et al.
Menopausal hormone replacement therapy and breast cancer: A meta-analysis.
Obstet Gynecol 1992;79:286-294

STANFORD JL, et al.
Combined estrogen and progestin hormone replacement therapy in relation to risk of breast cancer in middle-aged women.
JAMA 1995; 274 (2): 137-142

STEINBERG KK, et al.
A meta-analysis of the effect of estrogen replacement therapy on the risk of breast cancer.
JAMA 1991; 265 (15): 1985-1990

STEINGOLD KA, et al.
Treatment of hot flashes with transdermal estradiol administration.
J Clin Endocrinol Metab 1985; 61 (4): 627-632

SUREAU C, et al.
Objectif, qualité de vie! Les estrogènes: Une approche globale du traitement de la ménopause.
Sem Hop Paris 1989; 65 (36-37): 2225-2232

UTIAN WH.
Biosynthesis and physiologic effects of estrogen and pathophysiologic effects of estrogen deficiency:
A review.
Am J Obstet Gynecol 1989; 161: 1828-1831

VANDENBROUCKE JP, HELMERHORST FM.
Risk of venous thrombosis with hormone-replacement therapy
Lancet 1996; 348: 972.

WHITEHEAD MI, et al.
Endometrial responses to transdermal estradiol in postmenopausal women.
Am J Obstet Gynecol 1985; 152 (8): 1079-1084

WISEMAN L, McTAVISH D

Transdermal Estradiol-Norethisterone. A Review of its Pharmacological Properties and Clinical Use in Postmenopausal Women.
Drugs Aging, 1994; 4: 238-256

WINTER MI, and FRASER D.
Controversies concerning the safety of estrogen replacement therapy.
Am J Obstet Gynecol 1987; 56: 1313-1322

Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. Principal results from the Women's Health Initiative Randomised Controlled Trial.
JAMA. 2002; 288(3):321-333