IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0013/096/001
Case No: 2041044

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Novartis Pharmaceuticals Ltd

Frimley Business Park, **Frimley**, **Camberley**, **Surrey, GU16 7SR**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Estalis Sequi 50 micrograms/250 micrograms/24 hours, Transdermal Patch

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **06/03/2008**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Estalis Sequi 50 micrograms/250 micrograms/24 hours, Transdermal Patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Phase I
Each patch contains estradiol hemihydrate equivalent to 4.33 mg estradiol in a patch of 14.5 cm^2 releasing nominal 50 micrograms estradiol per 24 hours.

Phase II
Each patch contains estradiol hemihydrate equivalent to 0.51 mg estradiol and 4.80 mg norethisterone acetate in a patch of 16 cm^2 releasing nominal 50 micrograms estradiol and nominal 250 micrograms norethisterone acetate per 24 hours.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal patch.
Translucent round patches with a polymeric backing on one side and a release liner on the other side, packed individually in heat-sealed pouches.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Estalis Sequi 50/250 is indicated for:
- Hormone replacement therapy (HRT) for oestrogen deficiency symptoms in postmenopausal women.
- Prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis.
- Treatment is intended for women more than one year post menopause.

The experience of treating women older than 65 years is limited.

4.2 Posology and method of administration

Estalis Sequi 50 µg/250 µg/24 hours is a continuous sequential preparation for transdermal use. One treatment cycle of Estalis Sequi 50 µg/250 µg/24 hours consists of 4 Phase I transdermal patches followed by 4 Phase II transdermal patches. Therapy is started with the Phase I patch . The next treatment cycle should be started immediately after the removal of the last Phase II transdermal patch.
For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration (see section 4.4) should be used.

Initiation of therapy

Postmenopausal women who are not already receiving oestrogen-progestogen therapy may start using Estalis Sequi at any convenient time.

Women who are already using continuous combined oestrogen/progestogen therapy may be switched to Estalis Sequi 50 µg/250 µg/24 hours Phase I directly.

Women currently using cyclic or sequential oestrogen/progestogen therapy should complete the on-going treatment cycle before treatment with Estalis Sequi 50 µg/250 µg/24 hours Phase I is initiated.
The appropriate time to begin treatment with Estalis Sequi 50 µg/250 µg/24 hours Phase I would be the first day of a withdrawal bleeding.

General instructions

The Phase I transdermal patch is applied to the skin of the abdomen every 3 to 4 days for the first 14 days of a 28-day cycle. Thereafter, the Phase II transdermal patch is applied to the skin of the abdomen every 3 or 4 days for the remaining 14 days of the 28-day cycle. Women should be advised that monthly bleeding will usually occur.

Method of Administration

Care should be exercised when applying the patch. It must never be placed on or near the breasts. It should be placed on a clean, dry area of the abdomen which is not irritated, abraded or oily (i.e. should not be used with any moisturizing cream, lotion or oil). The waistline should be avoided, since tight clothing may rub the patch off.

The sites of application should be changed with an interval of at least one week allowed between applications to a particular site.

After opening the pouch, one half of the protective liner must be removed without touching the sticky side with the fingers. The transdermal patch must be applied to the skin immediately. The other half of the protective liner must be removed and the transdermal patch must be pressed firmly to the skin with the palm of the hand for at least 10 seconds, carefully smoothing down the edges.

Care should be taken during bathing or other activities so that the transdermal patch does not become dislodged. If the transdermal patch falls off (after strenuous physical activity, excessive sweating or friction from tight clothing), the same transdermal patch may be reapplied to another area. The original treatment should be thereafter followed, i.e. the transdermal patch should be exchanged on the same days as before.

Once in place, the transdermal patch should not be exposed to the sun for prolonged periods of time.

Should a patient forget 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 postmenopausal symptoms, break-through bleeding and spotting.

Should any adhesive remain after removal of the transdermal delivery system, the skin area should be gently rubbed with an oil-based cream or lotion.

4.3 Contraindications

Estalis Sequi 50 µg/250 µg/24 hours should not be used by women with any of the following conditions:
- Known, past or suspected breast cancer
- Known or suspected oestrogen-dependent malignant tumors (e.g.endometrial cancer)
- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
- Previous idiopathic or current venous thromboembolism (deep venous thrombosis, pulmonary embolism)
- Active or recent arterial thromboembolic disease (e.g. angina, myocardial infraction);
- Hypersensitivity to the active substances, or to any of the excipients (see section 6.1)
- Acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal
- Porphyria.

4.4 Special warnings and precautions for use

For the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and HRT should only continue as long as the benefit outweighs the risk.

Medical examination/follow-up

Before initiating or reinstituting HRT, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the section 4.3 and 4.4 . During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in the breasts should be reported to their doctor or nurse (see “Breast cancer” below). Investigations, including mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

Conditions which need supervision

If any of the following conditions are present, have occurred previously and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with Estalis Sequi 50 µg/250 µg/24 hours, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- A history of, or risk factors for thromboembolic disorders (see below)
- Risk factors for oestrogen dependent tumours, e.g. 1st degree heredity for breast cancer
- Hypertension
- Liver disorders (e.g. liver adenoma)
- Diabetes mellitus with or without vascular involvement
- Cholelithiasis
- Migraine or severe headache
- Systemic lupus erythematosus (SLE)
- A history of endometrial hyperplasia (see below)
- Epilepsy
- Asthma
- Otosclerosis

Reasons for immediate withdrawal of therapy

Therapy should be discontinued in case a contraindication is discovered and in the following situations:

- Jaundice or deterioration in liver function
- Significant increase in blood pressure
- New onset of migraine-like headache
- Pregnancy

Endometrial hyperplasia

- The risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administrated alone for prolonged periods (see section 4.8). The addition of a progestogen for at least 12 days per cycle in non-hysterectomised women greatly reduces this risk. Break-through bleeding and spotting may occur during the first months of treatment. If break-through bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.

Breast cancer

- A randomised placebo-controlled trial, the Women's Health Initiative study (WHI), and epidemiological studies, including the Million Women Study (MWS), have reported an increased risk of breast cancer in women taking oestrogens, oestrogen-progestogen combinations or tibolone for HRT for several years (see section 4.8.). For all HRT, an excess risk becomes apparent within a few years of use and increases with duration of intake but returns to baseline within a few (at most five) years after stopping treatment.

- In the MWS, the relative risk of breast cancer with conjugated equine estrogens (CEE) or estradiol (E2) was greater when a progestogen was added, either sequentially or continuously, and regardless of type of progestogen. There was no evidence of a difference in risk between the different routes of administration.

- In the WHI study, the continuous combined conjugated equine estrogens and medroxyprogesterone acetate (CEE + MPA) product used was associated with breast cancers that were slightly larger in size and more frequently had local lymph node metastases compared to placebo.

- HRT, especially oestrogen-progestogen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

Venous thromboembolism

- HRT is associated with a higher relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. One randomised controlled trial and epidemiological studies found a two- to threefold higher risk for users compared with non-users. For non-users, it is estimated that the number of cases of VTE that will occur over a 5-year period is about 3 per 1000 women aged 50-59 years and 8 per 1000 women aged between 60-69 years.

- It is estimated that in healthy women who use HRT for 5 years, the number of additional cases of VTE over a 5 year period will be between 2 and 6 (best estimate = 4) per 1000 women aged 50-59 years and between 5 and 15 (best estimate = 9) per 1000 women aged 60-69 years. The occurrence of such an event is more likely in the first year of HRT than later.

- Generally recognised risk factors for VTE include a personal history or family history, severe obesity (BMI > 30 kg/m^2) and systemic lupus erythematosus (SLE). There is no consensus about the possible role of varicose veins in VTE.

- Patients with a history of VTE or known thrombophilic states have an increased risk of VTE. HRT may add to this risk. Personal or strong family history of thromboembolism or recurrent spontaneous abortion should be investigated in order to exclude a thrombophilic predisposition. Until a thorough evaluation of thrombophilic factors has been made or anticoagulant treatment initiated, use of HRT in such patients should be viewed as contraindicated. Those women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.

- The risk of VTE may be temporarily increased with prolonged immobilisation, major trauma or major surgery. As in all postoperative patients, scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Where prolonged immobilisation is liable to follow elective surgery, particularly abdominal or orthopaedic surgery to the lower limbs, consideration should be given to temporarily stopping HRT 4 to 6 weeks earlier, if possible. Treatment should not be restarted until the woman is completely mobilised.

- If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctor immediately when they are aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnea).

Coronary artery disease (CAD)

- There is no evidence from randomised controlled trials of cardiovascular benefit with continuous combined conjugated oestrogens and medroxyprogesterone acetate (MPA). Two large clinical trials (WHI and HERS i.e. Heart and Estrogen/progestin Replacement Study) showed a possible increased risk of cardiovascular morbidity in the first year of use and no overall benefit. For other HRT products there are only limited data from randomised controlled trials examining effects in cardiovascular morbidity or mortality. Therefore, it is uncertain whether these findings also extend to other HRT products.

Stroke

- One large randomised clinical trial (WHI-trial) found, as a secondary outcome, an increased risk of ischemic stroke in healthy women during treatment with continuous combined conjugated oestrogens and MPA. For women who do not use HRT, it is estimated that the number of cases of stroke that will occur over a 5-year period is about 3 per 1000 women aged 50 to 59 years and 11 per 1000 women aged 60 to 69 years.

- It is estimated that for women who use conjugated oestrogens and MPA for 5 years, the number of additional cases will be between 0 and 3 (best estimate = 1) per 1000 users aged 50 to 59 years and between 1 and 9 (best estimate = 4) per 1000 users aged 60 to 69 years. It is unknown whether the increased risk also extends to other HRT products.

Ovarian cancer

- Long-term (at least 5 to 10 years) use of oestrogen-only HRT products in hysterectomised women has been associated with an increased risk of ovarian cancer in some epidemiological studies. It is uncertain whether long-term use of combined HRT confers a different risk than oestrogen-only products.

Other conditions

- Oestrogens may cause fluid retention and therefore women with cardiac or renal dysfunction should be carefully observed. Women with terminal renal insufficiency should be closely observed, since it is expected that the level of circulating active ingredients of Estalis Sequi 50 µg/250 µg/24 hours is increased.

- Women with pre-existing hypertriglyceridemia should be followed closely during oestrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oral oestrogen therapy in this condition.

- Oestrogens increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radio-immunoassay) or T3 levels (by radio-immunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Other binding proteins may be elevated in serum, i.e. corticoid binding globulin (CBG), sex-hormone-binding globulin (SHBG) leading to increased circulating corticosteroids and sex steroids, respectively. Free or biological active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-I-antitrypsin, ceruloplasmin).

- There is no conclusive evidence for improvement of cognitive function. There is some evidence from the WHI trial of increased risk of probable dementia in women who start using continuous combined CEE and MPA after the age of 65. It is unknown whether the findings apply to younger postmenopausal women or other HRT products.

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

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of oestrogens and progestogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepine), and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz). Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones.
Herbal preparations containing St. John's wort (*Hypericum Perforatum*) may induce the metabolism of oestrogens and progestogens.
At transdermal administration, the first-pass effect in the liver is avoided and, thus, transdermally applied oestrogens and progestogens might be less affected than oral hormones by enzyme inducers.

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

4.6 Pregnancy and lactation

Pregnancy
Estalis Sequi 50 µg/250 µg/24 hours is not indicated during pregnancy. If pregnancy occurs during medication with Estalis Sequi 50 µg/250 µg/24 hours treatment should be withdrawn immediately.
Data on a limited number of exposed pregnancies indicate no adverse effects of norethisterone acetate on the foetus. At doses higher than normally used in oral contraceptives and HRT formulations masculinisation of female foetuses was observed.
The results of most epidemiological studies to date relevant to inadvertent foetal exposure to combinations of oestrogens and progestogens indicate no teratogenic or foetotoxic effect.

Lactation
Estalis Sequi 50 µg/250 µg/24 hours is not indicated during lactation.

4.7 Effects on ability to drive and use machines

Estalis Sequi 50 µg/250 µg/24 hours has no known effects on the ability to drive and use machines.

4.8 Undesirable effects

Approximately one third of the women treated with Estalis Sequi 50 µg/250 µg/24 hours can be expected to experience adverse reactions. The most commonly reported adverse experiences are breast tension and pain (31%), application site reactions (20% mostly mild erythema), dysmenorrhoea (19%), irregular bleeding (16%)and headache (10%).

Table 1:
Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥ 1/10,000 to < 1/1,000); Very rare (< 1/10,000)

Investigations	
Uncommon	Transaminases increase
Nervous system disorders	
Very common	Headache
Common	Dizziness, nervousness, insomnia, mood changes
Uncommon	Migraine, vertigo
Gastrointestinal disorders	
Common	Nausea, flatulence, diarrhoea, dyspepsia, abdominal pain
Uncommon	Vomitting

Skin and subcutaneous tissue disorders	
Very common	Application site reactions
Common	Acne, rash, pruritus, dry skin
Uncommon	Skin discoloration
Musculoskeletal and connective tissue disorders	
Common	Back pain, pain in extremity
Rare	Myasthenia
Vascular disorders	
Uncommon	Increase in blood pressure, varicose veins
Rare	Venous thromboembolism
General disorders and administration site conditions	
Common	Pain, asthenia, weight changes, peripheral oedema
Rare	Allergic reactions, libido changes, paraesthesia
Hepatobiliary disorders	
Rare	Gallstones, gallbladder disease
Very rare	Cholestatic jaundice
Reproductive system and breast disorders	
Very common	Breast pain, breast tenderness, dysmenorrhoea, menstrual disorder
Common	Breast enlargement, menorrhagia, leucorrhoea, irregular vaginal bleeding, uterine spasms, vaginitis, endometrial hyperplasia
Uncommon	Breast cancer
Rare	Uterine leiomyomata, paratubular cysts, endocervical polyps
Psychiatric disorders	
Common	Depression

Breast cancer

According to evidence from a large number of epidemiological studies and one randomised placebo-controlled trial, the Women's Health Initiative (WHI), the overall risk of breast cancer increases with increasing duration of HRT use in current or recent HRT users.

For *oestrogen-only* HRT, estimates of relative risk (RR) from a reanalysis of original data from 51 epidemiological studies (in which >80% of HRT use was oestrogen-only HRT) and from the epidemiological Million Women Study (MWS) are similar at 1.35 (95%CI 1.21 – 1.49) and 1.30 (95%CI 1.21 – 1.40), respectively.

For *oestrogen plus progestogen* combined HRT, several epidemiological studies have reported an overall higher risk for breast cancer than with oestrogens alone.

The MWS reported that, compared to never users, the use of various types of oestrogen-progestogen combined HRT was associated with a higher risk of breast cancer (RR = 2.00, 95%CI: 1.88 – 2.12) than use of oestrogens alone (RR = 1.30, 95%CI: 1.21 – 1.40) or use of tibolone (RR=1.45; 95%CI 1.25-1.68).

The WHI trial reported a risk estimate of 1.24 (95%CI 1.01 – 1.54) after 5.6 years of use of oestrogen-progestogen combined HRT (CEE + MPA) in all users compared with placebo.

The absolute risks calculated from the MWS and the WHI trial are presented below:

The MWS has estimated, from the known average incidence of breast cancer in developed countries, that:
- For women not using HRT, about 32 in every 1000 are expected to have breast cancer diagnosed between the ages of 50 and 64 years.
- For 1000 current or recent users of HRT, the number of additional cases during the corresponding period will be:
- For users of oestrogen-only replacement therapy
- between 0 and 3 (best estimate = 1.5) for 5 years' use,
- between 3 and 7 (best estimate = 5) for 10 years' use.
- For users of oestrogen plus progestogen combined HRT
- between 5 and 7 (best estimate = 6) for 5 years' use,
- between 18 and 20 (best estimate = 19) for 10 years' use.

The WHI trial estimated that after 5.6 years of follow-up of women between the ages of 50 and 79 years, an *additional* 8 cases of invasive breast cancer would be due to *oestrogen-progestogen combined* HRT (CEE + MPA) per 10,000 women years.

According to calculations from the trial data, it is estimated that:
- For 1000 women in the placebo group, about 16 cases of invasive breast cancer would be diagnosed in 5 years.
- For 1000 women who used oestrogen + progestogen combined HRT (CEE + MPA), the number of *additional* cases would be between 0 and 9 (best estimate = 4) for 5 years' use.

The number of additional cases of breast cancer in women who use HRT is broadly similar for women who start HRT irrespective of age at start of use (between the ages of 45-65) (see section 4.4).

Endometrial cancer

In women with an intact uterus, the risk of endometrial hyperplasia and endometrial cancer increases with increasing duration of use of unopposed oestrogens. According to data from epidemiological studies, the best estimate of the risk is that for women not using HRT, about 5 in every 1000 are expected to have endometrial cancer diagnosed between the ages of 50 and 65. Depending on the duration of treatment and oestrogen dose, the reported increase in endometrial cancer risk among unopposed oestrogen users varies from 2-to 12-fold greater compared with non-users. Adding a progestogen to oestrogen-only therapy greatly reduces this increased risk.

Other adverse reactions have been reported in association with oestrogen-progestogen treatments:
- Oestrogen-dependent neoplasms benign and malignant, e.g. endometrial cancer
- Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism, is more frequent among hormone replacement therapy users than among non-users (see section 4.3 and section 4.4)
- Myocardial infarction and stroke
- Gall bladder disease
- Skin and subcutaneous disorders: chloasma, erythema multiform, erythema nodosum, vascular purpura
- Probable dementia (see section 4.4)

4.9 Overdose

Due to the mode of administration, overdose of estradiol or norethisterone is unlikely to occur. If signs of overdose appear the Estalis Sequi 50 µg/250 µg/24 hours transdermal patch should be removed. The effects of overdosage with oral oestrogens are breast tenderness, nausea, vomiting and/or metrorrhagia. Overdosage of progestogens may lead to a depressive mood, fatigue, acne and hirsutism.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeuticgroup: Genito urinary system and sex hormones
ATC code: G03FB05.

The active ingredient, estradiol hemihydrate, a synthetic 17β-estradiol, is chemically and biologically identical to endogenous human estradiol. It substitutes for the loss of oestrogen production in menopausal women, and alleviates menopausal symptoms.
Oestrogens prevent bone loss following menopause or ovariectomy.

As oestrogens promote the growth of the endometrium, unopposed oestrogens increase the risk of endometrial hyperplasia and cancer. The addition of norethisterone acetate, a progestogen, reduces the oestrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

Information from clinical trials

- Relief of oestrogen-deficiency symptoms and bleeding patterns:

Relief of menopausal symptoms was achieved during the first few weeks of treatment.
Regular withdrawal bleeding occurred in 64 % of women after 11 treatment cycles with Estalis Sequi 50 µg/250 µg/24 hours. Irregular bleeding and/or spotting were reported in 28 %, and amenorrhea in 8 %.

- Prevention of osteoporosis

Oestrogen deficiency at menopause is associated with an increasing bone turnover and decline in bone mass. The effect of oestrogens on the bone mineral density is dose-dependent. Protection appears to be effective for as long as treatment is continued. After discontinuation of HRT, bone mass is lost at a rate similar to that in untreated women.

Evidence from the WHI trial and meta-analysed trials shows that current use of HRT, alone or in combination with a progestogen – given to predominantly healthy women – reduces the risk of hip, vertebral, and other osteoporotic fractures. HRT may also prevent fractures in women with low bone density and/or established osteoporosis, but the evidence for that is limited.

After two years of treatment with Estalis Sequi 50 µg/250 µg/24 hours, the increase in lumbar spine bone mineral density (BMD) was 5.53%± 0.63 % (mean ± SD). The percentage of women who maintained or gained BMD in lumbar zone during treatment was 95.0%.
Estalis Sequi 50 µg/250 µg/24 hours also had an effect on hip BMD. The increase after two years was 3.07% ± 0.64% (mean ± SD) at femoral neck and 3.12% ± 0.46% (mean ± SD) at total hip.

5.2 Pharmacokinetic properties

Absorption

Transdermally delivered estradiol bypasses the first pass effect seen with orally administered oestrogen products.

Estradiol: Estalis Sequi 50 µg/250 µg/24 hours transdermal patch achieves estradiol serum levels and estrone/estradiol ratios in the range of those observed in premenopausal women at the early (estradiol > 40 pg/ml) to mid-follicular phase. These characteristics are maintained for an entire 84 to 96 hour wear period. Repeated application of the Estalis Sequi Phase I patch resulted in steady-state maximum estradiol serum concentration (C_{max}) of 71 pg/ml and average estradiol serum concentration (C_{avg}) of 51 pg/ml. At the end of the application periods, the mean serum estradiol concentration (trough concentration) was 41 pg/ml.

Repeated application of the Estalis Sequi Phase II patch resulted in steady-state maximum estradiol serum concentration (C_{max}) of 71 pg/ml and average estradiol serum concentration (C_{avg}) of 51 pg/ml. At the end of the application periods, the mean serum estradiol concentration (trough concentration) was 46 pg/ml.

Norethisterone acetate: Repeated application of Estalis Sequi Phase II patches resulted in steady-state maximum serum norethisterone concentration (C_{max}) of 1060 pg/ml and average serum norethisterone concentration (C_{avg}) of 832 pg/ml. At the end of the application periods, the mean serum concentration of norethisterone was 681 pg/ml.

Metabolism and elimination
Estradiol: Estradiol has a short elimination half-life of approximately 2 to 3 hours, which means that serum levels quickly drop when the transdermal patch is removed. After the transdermal patch has been removed, serum estradiol concentrations return to untreated postmenopausal levels (< 20 pg/ml) within 4 to 8 hours.
Norethisterone: The elimination half-life of norethisterone is reported to be 6 to 8 hours. After removal of the Estalis Sequi Phase II patch, serum norethisterone concentrations diminish rapidly and are less than 50 pg/ml within 48 hours.

Minimal fluctuations in serum estradiol and norethisterone concentrations demonstrate consistent deliveries over the application interval.

There is no accumulation of estradiol or norethisterone in the circulation following multiple applications.

5.3 Preclinical safety data

The acute toxicity of estrogens is low. Because of marked differences between animal species and between animals and humans preclinical results possess a limited predictive value for the application of estrogens in humans.

In experimental animals estradiol or estradiol valerate displayed an embryo lethal effect already at relatively low doses; malformations of the urogenital tract and feminisation of male foetuses were observed.

Norethisterone, like other progestogens, caused virilisation of female foetuses in rats and monkeys. After high doses of norethisterone embryo lethal effects were observed.

Non-clinical data based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenic potential revealed no particular human risks beyond those discussed in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Estalis Sequi Phase I
Acrylic adhesive
Rubber-based synthetic adhesive
Polyisobutylene
Oleic acid
Bentonite
Ethylene vinyl acetate resin
1,3-Butanediol
Mineral oil
Dipropylene glycol
Lecithin/propylene glycol mixture.

The backing layer consists of a polyurethane/ethylene vinyl alcohol copolymer film. The protective (release) liner is a silicone-coated polyester film.

Estalis Sequi Phase II
Silicone adhesives
Acrylic adhesives
Povidone
Oleic acid
Dipropylene glycol

The backing layer consists of a polyester film laminate. The protective (release) liner is a fluoropolymer coated polyester film.

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

24 months: 18 months stored in a refrigerator (2°C to 8° C) plus 6 months stored below 25° C.

6.4 Special precautions for storage

Store and transport refrigerated (2°C -8°C). Do not freeze. Once dispensed to the patient, Estalis Sequi 50 micrograms/250 micrograms/24 hours may be stored below 25°C for a maximum period of 6 months. Store in the original (sealed) pouch. Each patch should be used immediately after opening the pouch.

6.5 Nature and contents of container

Estalis Sequi 50 micrograms/250 micrograms/24 hours transdermal patches are packed individually in heat-sealed paper/polyethylene sachets.
Estalis Sequi 50 micrograms/250 micrograms/24 hours pack consists of 4 or 12 Phase I round transdermal patches each containing estradiol hemihydrate equivalent to 4.33 mg estradiol and 4 or 12 Phase II round transdermal patches, each containing estradiol hemidhydrate equivalent to 0.51 mg estradiol and 4.80 mg norethisterone acetate.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Used patches should be folded in half with adhesive surfaces pressed together and discarded safely and away from the reach and sight of children.

7 MARKETING AUTHORISATION HOLDER

Novartis Pharmaceuticals Limited
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Frimley
Camberley
Surrey GU16 7SR
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 0013/096/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 October 1998
Date of last renewal: 06 March 2008

10 DATE OF REVISION OF THE TEXT

March 2009