IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0013/096/002
Case No: 2044026

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

Novartis Pharmaceuticals UK 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

Sequidot 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 **23/01/2008** until **22/02/2012**.

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

SEQUIDOT, transdermal patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Phase I
Each patch contains estradiol hemihydrate equivalent to 0.78 mg estradiol in a patch of 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 50 micrograms estradiol and 250 micrograms norethisterone acetate per 24 hours.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal patch.

Phase I
Translucent square patches with rounded corners, with a polymeric backing layer on one side and an adhesive layer, releasing the active substances on the other side. Individually packed in heat-sealed pouches.

Phase II
Translucent round patches, with a polymeric backing layer on one side and an adhesive layer, releasing the active substances on the other side. Individually packed in heat-sealed pouches.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- 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

Sequidot is a continuous sequential preparation for transdermal use.
One treatment cycle of Sequidot 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 also section 4.4) should be used.

Initiation of therapy

The treatment regimen may be initiated at any convenient time for most menopausal women who are not currently using any oestrogen/progestagen therapy.

Women who are already using continuous combined oestrogen/progestagen therapy may be switched to Sequidot directly.

Women currently using cyclical or sequential oestrogen/progestogen therapy should complete the ongoing treatment cycle before treatment with Sequidot Phase I is initiated. The appropriate time to begin treatment with Sequidot Phase I is 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 during 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 to 4 days during the remaining 14 days of the 28-day cycle.

Women should be informed that monthly bleeding usually occurs.

Administration

The transdermal patch should be placed on the abdomen. It must never be applied on or near the breasts. Care should be exercised when applying the patch. It should be placed on a clean, dry, area of the abdomen which is free from cuts and irritation. The skin area should not be oily, i.e. the patch should not be used with any moisturising cream, lotion, or oil. The waistline should be avoided, as tight clothing may cause the patch to rub 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 film 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 film 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.

Patients should be alerted to take care that the transdermal patch does not become dislodged during bathing or during other activities. They should also be informed that in the event of a transdermal patch falling off (after strenuous physical activity, excessive sweating, or friction from tight-fitting clothing), the same patch may be re-applied to another area of skin. Thereafter patients should resume treatment as usual and replace the patch on the same days as before.

Patients should be informed that, once in place, the patch should not be exposed to sunlight for any 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, breakthrough bleeding, and spotting.

Should any adhesive remain on the skin after the patch has been removed, the area should be gently rubbed with an oil-based cream or lotion to remove the sticky residues.

4.3 Contraindications

- Known, past or suspected breast cancer;
- Known or suspected oestrogen-dependent malignant tumours (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 infarction);
- Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal;
- Known hypersensitivity to the active substances, or to any of the excipients of Sequidot, such as dipropylene glycol (which may cause skin irritations);
- 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 be continued 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 sections 4.3 Contraindications and 4.4 Special warnings and precautions for use. 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 Sequidot, 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-type headache;
- Pregnancy.

Endometrial hyperplasia
The risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods (see section 4.8). The addition of a progestagen 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-progestagen 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 oestrogens (CEE) or estradiol (E2) was greater when a progestagen was added, either sequentially or continuously, and regardless of type of progestagen. There was no evidence of a difference in risk between the different routes of administration.
In the WHI study, the continuous combined conjugated equine oestrogens 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-progestagen 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, dyspnoea).

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 Oestrogen/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 ischaemic 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 50-59 years and 11 per 1000 women aged 60-69 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 50-59 years and between 1 and 9 (best estimate = 4) per 1000 users aged 60-69 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 estradiol and norethisterone 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 progestagens 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 progestagens.

At transdermal administration, the first-pass effect in the liver is avoided and, thus, transdermally applied oestrogens and progestagens might be less affected than oral hormones by enzyme inducers.

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

4.6 Pregnancy and lactation

Pregnancy
Sequidot is not indicated during pregnancy. If pregnancy occurs during medication with Sequidot, treatment should be withdrawn immediately. Clinically, 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 progestagens indicate no teratogenic or foetotoxic effect.

Lactation
Sequidot is not indicated during lactation.

4.7 Effects on ability to drive and use machines

No known effects on the ability to drive and use machines.

4.8 Undesirable effects

Approximately one third of the women treated with Sequidot can be expected to experience adverse reactions. The most commonly reported adverse effects are breast tension and pain (31%), application site reactions (20% mostly mild erythema), dysmenorrhoea (19%), irregular menstruation (16%), and headache (10%).

The following adverse effects have been observed:

Organ Class	Very common (≥1/10)	Common (≥1/100; < 1/10)	Uncommon (≥ 1/1000; < 1/100)	Rare (≥ 1/10,000; < 1/1000)	Very rare (< 1/10,000)
Immune system disorders					Urticaria, anaphylactic reaction
Metabolism and nutrition disorders					Decreased carbohydrate tolerance
Psychiatric disorders		Depression			

Nervous system disorders	Headache	Nervousness, mood changes, insomnia	Migraine, dizziness	Paraesthesia	Chorea
Eye disorders					Contact lens intolerance
Vascular disorders			Increase in blood pressure	Vein thrombo-embolism	
Gastrointestinal disorders		Nausea, dyspepsia, diarrhoea, abdominal pain, bloating	Vomiting		
Hepatobiliary disorders				Gallbladder disease, gallstones	Cholestatic jaundice
Skin and subcutaneous tissue disorders	Application site reactions, erythema	Acne, rash, pruritus, dry skin	Skin discoloration	Alopecia	Hirsutism, skin necrosis
Musculoskeletal and connective tissue disorders				Myasthenia	
Reproductive system and breast disorders	Breast tension and pain, dysmenorrhoea, menstrual disorders	Breast enlargement, menorrhagia, leucorrhoea, irregular vaginal bleeding, uterine spasm, vaginitis, endometrial hyperplasia		Uterine myoma, paratubular cysts, cervical polyps	
General disorders and administration site conditions		Pain, back pain, asthenia, peripheral oedema, weight changes		Libido changes, allergic reactions	
Investigations			Transaminases increase		

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 progestagen* 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-progestagen 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 HRT (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-progestagen combined HRT (CEE + MPA) in all users compared with placebo.

The absolute risks calculated from the MWS and the WHI trials 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 progestagen 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-progestagen 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 + progestagen 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 oestrogens without addition of a progestagen. 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 varies from 2-to 12-fold greater compared with non-users. Adding a progestagen to oestrogen- only therapy greatly reduces this increased risk.

Other adverse reactions have been reported in association with oestrogen-progestagen 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. For further information, see section 4.3 Contraindications and 4.4 Special warnings and special precautions for use;
- Myocardial infarction and stroke;
- Gall bladder disease;
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura;
- Probable dementia (see section 4.4).

4.9 Overdose

Due to the mode of administration, overdose of estradiol or norethisterone acetate is unlikely to occur. If signs of overdose appear, the transdermal patch should be removed from the skin. Symptoms of overdosage in oral oestrogen therapy are breast tenderness, nausea, vomiting, and/or metrorrhagia. Overdosage of progestogen may lead to depressive mood, fatigue, acne, and hirsutism.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestagens and oestrogens, sequential preparations, norethisterone and oestrogen. ATC code G03FB05

The active ingredient, 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 progestagen, 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 Sequidot. Irregular bleeding and/or spotting was reported in 28% and amenorrhoea 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 progestagen – 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 Sequidot, 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%.
Sequidot 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 administered estradiol does not undergo the first-pass effect seen with orally adminstered oestrogen products.

Estradiol: Sequidot transdermal patches produce serum levels of estradiol and estrone/estradiol ratios in the range normally observed in premenopausal women at the early (estradiol > 40 pg/ml) to mid follicular phase. These characteristics are maintained for the entire 84 to 96 hour wear period. Repeated application of Estalis Sequi Phase I (50/0 micrograms/day) patches, which are bioequivalent to Sequidot Phase I patches, 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 interval, the mean serum estradiol concentration (trough concentration) was 41 pg/ml.

Repeated application of Sequidot Phase II (50/250 micrograms/day) patches resulted in steady state maximum estradiol serum concentration (C_{max}) of 71 pg/ml and average estradiol concentration (C_{avg}) of 52 pg/ml. At the end of the application interval, the mean serum estradiol concentration (trough concentration) was 46 pg/ml.

Norethisterone acetate: Repeated application of Sequidot resulted in steady state maximum serum norethisterone concentration (C_{max}) of 1060 pg/ml and average (C_{avg}) serum norethisterone concentration of 832 pg/ml. At the end of the application interval, the mean serum norethisterone concentration (trough concentration) was 681 pg/ml.

Metabolisation and elimination

Estradiol: Estradiol has a short elimination half-life of around 2 to 3 h, which means that serum levels quickly drop when the patch is removed. After the patch has been removed, serum estradiol concentrations return to untreated postmenopausal levels (< 20 pg/ml) within 4-8 hours.

Norethisterone: Norethisterone has a reported elimination half-life of around 6 to 8 hours. Serum norethisterone levels drop rapidly when the patch is removed, falling to less than 50 pg/ml within 48 hours.

Minimal fluctuations in the serum concentrations of estradiol and norethisterone show consistent release over the application interval

There is no accumulation of estradiol and norethisterone after repeated application.

5.3 Preclinical safety data

The acute toxicity of oestrogens is low. As there are considerable differences among animal species and between animal species and man, preclinical data on oestrogens are of limited applicability to man.

Animal studies of estradiol and estradiol valerate have shown lethal effects on the embryo already at relatively low doses; malformation of the urogenital tract and feminisation of male fetuses were observed. Norethisterone, like other progestagens, caused virilisation of female fetuses in rats and monkeys. After high doses of norethisterone acetate embryolethal effects were observed (see also section 4.6).

Preclinical data revealed no special hazard for humans based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential and toxicity to reproduction beyond data included in other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Phase I
Adhesive matrix:
acrylic and silicone adhesive matrix
oleyl alcohol
dipropylenic glycol
povidone

Backing layer:
co-extruded film of ethylene/vinyl acetate copolymer
polyethylene
vinylidene/vinyl chloride copolymer
silicon dioxide/titanium dioxide

Release liner:
fluoropolymer-coated polyester film

Phase II
Adhesive matrix:
acrylic and silicone adhesive matrix
povidone
oleic acid
dipropylene glycol

Backing layer:
polyester film

Release liner:
fluoropolymer-coated polyester film

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

The shelf life is 2 years; 18 months stored in a refrigerator (2-8ºC) plus 6 months below 25ºC.

6.4 Special precautions for storage

Store and transport refrigerated (2-8ºC). Do not freeze.
Once dispensed to the patient, Sequidot 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

The transdermal patches are individually packed in heat-sealed paper/polyethylene/ pouches.

Pouches are provided in cartons of 8 patches (4 Phase I and 4 Phase II patches) or 24 patches (12 Phase I and 12 Phase II patches).

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

Norvartis Pharmaceuticals UK Ltd
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8 MARKETING AUTHORISATION NUMBER

PA13/96/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23rd February 2007

10 DATE OF REVISION OF THE TEXT