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 five 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 the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Transdermal patch.

Phase I
Translucent rectangular 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. (see also section 4.4)

Treatment is intended for women with at least 6 months since their last menses.

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/progestagen 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.

Method of 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 or current venous thromboembolism (deep venous thrombosis, pulmonary embolism);
- Known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency, see section 4.4);
- 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 listed in section 6.1, 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.

Evidence regarding the risks associated with HRT in the treatment of premature menopause is limited. Due to the low level of absolute risk in younger women, however, the balance of benefits and risks for these women may be more favourable than in older women.

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 their breasts should be reported to their doctor or nurse (see 'Breast cancer' below). Investigations, including appropriate imaging tools, e.g. 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
- 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 and carcinoma

In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among oestrogen-only users varies from 2-to 12-fold greater compared with non-users, depending on the duration of treatment and oestrogen dose (see section 4.8). After stopping treatment risk may remain elevated for at least 10 years.

The addition of a progestagen cyclically for at least 12 days per month/28 day cycle or continuous combined oestrogen-progestagen therapy in non-hysterectomised women prevents the excess risk associated with oestrogen-only HRT.

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

The overall evidence shows an increased risk of breast cancer in women taking combined oestrogen progestagen or oestrogen-only HRT, that is dependent on the duration of taking HRT.

Combined oestrogen-progestagen therapy

- The randomised placebo-controlled trial, the Women's Health Initiative study (WHI), and a meta-analysis of prospective epidemiological studies are consistent in finding an increased risk of breast cancer in women taking combined oestrogen-progestagen for HRT that becomes apparent after about 3 (1-4) years (see section 4.8).

Oestrogen-only therapy

- The WHI trial found no increase in the risk of breast cancer in hysterectomised women using oestrogen-only HRT. Observational studies have mostly reported a small increase in risk of having breast cancer diagnosed that is lower than that found in users of oestrogen-progestagen combinations (see section 4.8).

Results from a large meta-analysis showed that after stopping treatment, the excess risk will decrease with time and the time needed to return to baseline depends on the duration of prior HRT use. When HRT was taken for more than 5 years, the risk may persist for 10 years or more.

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

Ovarian cancer

Ovarian cancer is much rarer than breast cancer.
Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking oestrogen-only or combined oestrogen-progestagen HRT, which becomes apparent within 5 years of use and diminishes over time after stopping.
Some other studies, including the WHI trial, suggest that the use of combined HRTs may be associated with a similar or slightly smaller risk (see Section 4.8).

Venous thromboembolism

- HRT is associated with a 1.3-3 fold risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of HRT than later (see Section 4.8).

- Generally recognised risk factors for VTE include use of oestrogens, older age, major surgery, prolonged immobilisation, obesity (BMI > 30 kg/m^2), pregnancy/postpartum period, systemic lupus erythematosus (SLE) and cancer. There is no consensus about the possible role of varicose veins in VTE.

- Patients with known thrombophilic states have an increased risk of VTE and HRT may add to this risk. HRT is therefore contraindicated in these patients (see section 4.3).

- Women already on chronic anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.

- As in all postoperative patients, prophylactic measures need be considered to prevent VTE following surgery. If prolonged immobilisation is to follow elective surgery, temporarily stopping HRT 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilised.

- In women with no personal history of VTE but with a first degree relative with a history of thrombosis at young age, screening may be offered after careful counselling regarding its limitations (only a proportion of thrombophilic defects are identified by screening). If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is ‘severe’ (e.g., antithrombin, protein S, or protein C deficiencies or a combination of defects) HRT is contraindicated.

- If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors 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 protection against myocardial infarction in women with or without existing CAD who received combined oestrogen-progestagen or oestrogen-only HRT.

Combined oestrogen-progestagen therapy

The relative risk of CAD during use of combined oestrogen-progestagen HRT is slightly increased. As the baseline absolute risk of CAD is strongly dependent on age, the number of extra cases of CAD due to oestrogen-progestagen use is very low in healthy women close to menopause, but will rise with more advanced age.

Oestrogen-only

Randomised controlled data found no increased risk of CAD in hysterectomised women using oestrogen-only therapy.

Ischaemic stroke

- Combined oestrogen-progestagen and oestrogen-only therapy are associated with an up to 1.5-fold increase in risk of ischaemic stroke. The relative risk does not change with age or time since menopause. However, as the baseline risk of stroke is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age (see section 4.8).

Hypothyroidism

- Patients who require thyroid hormone replacement therapy should have their thyroid function monitored regularly while on HRT to ensure that thyroid hormone levels remain in an acceptable range.

Severe anaphylactic/anaphylactoid reactions

- Cases of anaphylactic/anaphylactoid reactions, which developed anytime during the course of estradiol treatment and required emergency medical management, have been reported in the post marketing setting.

Other conditions

Oestrogens may cause fluid retention and therefore patients with cardiac or renal dysfunction should be carefully observed.

Women with pre-existing hypertriglyceridaemia 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).

- HRT use does not improve cognitive function. There is some evidence of increased risk of probable dementia in women who start using continuous combined or oestrogen-only HRT after the age of 65.

- 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.

- Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.

ALT elevations
During clinical trials with patients treated for hepatitis C virus (HCV) infections with the combination regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medicinal products such as combined hormonal contraception (CHCs). Additionally, also in patients treated with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs.
Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol, and ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of women taking these other oestrogens, caution is warranted for co-administration with the following combination drug regimens: ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin; glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir (see section 4.5).

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, telaprevir 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.

Estradiol is predominantly metabolized by CYP3A4, hence concomitant administration of inhibitors of CYP3A4 such as ketoconazole, erythromycin may result in increase in the exposure of estradiol.

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 effect and changes in the uterine bleeding profile.

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

Pharmacodynamic interactions

Direct acting antiviral agents (DAAs) and ethinylestradiol-containing medicinal products such as CHCs

During clinical trials with the HCV combination drug regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medicinal products such as CHCs. Additionally, also in patients treated with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs.

Direct acting antiviral agents (DAAs) and medicinal products containing oestrogens other than ethinylestradiol, such as estradiol

Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol, and ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of women taking these other oestrogens, caution is warranted for co-administration with the following combination drug regimens: ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin; glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir (see section 4.4).

Effect of HRT with oestrogens on other medicinal products
Hormone contraceptives containing oestrogens have been shown to significantly decrease plasma concentrations of lamotrigine when co-administered due to induction of lamotrigine glucuronidation. This may reduce seizure control. Although the potential interaction between hormone replacement therapy and lamotrigine has not been studied, it is expected that a similar interaction exists, which may lead to a reduction in seizure control among women taking both medicinal products together.

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 effects.

Breast-feeding
Sequidot is not indicated during breast-feeding.

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:

Table 1:
Within each frequency grouping, adverse drug reactions are presented in the order of decreasing seriousness. 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); not known (cannot be estimated from the available data).

System organ class (MedDRA SOC level)	***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)***	***Not known**** *(cannot be estimated from the available data)*

Immune system disorders				Hypersensitivity		Anaphylactic reaction, anaphylactoid reaction
Metabolism and nutrition disorders					Decreased carbohydrate tolerance	
Psychiatric disorders		Depression, nervousness, affect lability		Libido disorder		
Nervous system disorders	Headache	Insomnia	Migraine, dizziness	Paraesthesia	Chorea	
Eye disorders					Contact lens intolerance	
Vascular disorders			Blood pressure increased	Embolism venous		Varicose veins
Gastrointestinal disorders		Nausea, diarrhoea, dyspepsia, abdominal pain, abdominal distension	Vomiting			
Hepatobiliary disorders				Gallbladder disorder, cholelithiasis	Jaundice cholestatic	
Skin and subcutaneous tissue disorders	Application site reactions†, erythema	Acne, rash, pruritus, dry skin	Skin discoloration	Alopecia	Hirsutism, skin necrosis	Contact dermatitis
Musculoskeletal and connective tissue disorders		Back pain		Myasthenia		Pain in extremity
Reproductive system and breast disorders	Breast tension and pain, dysmenorrhoea, menstrual disorder	Breast enlargement, menorrhagia, genital discharge, irregular vaginal bleeding, uterine spasms, vaginal infection, endometrial hyperplasia		Uterine leiomyoma, fallopian tube cysts, cervical polyps		
General disorders and administration site conditions		Pain, asthenia, oedema peripheral, weight increased				
Investigations			Transaminases increased			

(*) Reported in post-marketing experience.

(†) Application site reactions includes localized bleeding, bruising, burning, discomfort, dryness, eczema, edema, erythema, inflammation, irritation, pain, papules, paraesthesia, pruritus, rash, skin discolouration, skin pigmentation, swelling, urticaria, and vesicles.

Breast cancer risk

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestagen therapy for more than 5 years.
- The increased risk in users of oestrogen-only therapy is lower than that seen in users of oestrogen-progestagen combinations.
- The level of risk is dependent on the duration of use (see section 4.4).
- Absolute risk estimations based on results of the largest randomised placebo-controlled trial (WHI-study) and the largest meta-analysis of prospective epidemiological studies are presented.

Largest meta-analysis of prospective epidemiological studies – Estimated additional risk of breast cancer after 5 years' use in women with BMI 27 (kg/m^2)

Age at start HRT (years)	Incidence per 1000 never-users of HRT over a 5 year period (50-54 years)*	Risk ratio	Additional cases per 1000 HRT users after 5 years
		Oestrogen only HRT	
50	13.3	1.2	2.7
		Combined oestrogen-progestagen	
50	13.3	1.6	8.0

* Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m^2).
Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.

Estimated additional risk of breast cancer after 10 years' use in women with BMI 27 (kg/m^2)

Age at start HRT (years)	Incidence per 1000 never-users of HRT over a 10 year period (50-59 years)*	Risk ratio	Additional cases per 1000 HRT users after 10 years
		Oestrogen only HRT	
50	26.6	1.3	7.1
		Combined oestrogen-progestagen	
50	26.6	1.8	20.8

* Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m^2).
Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.

US WHI studies - additional risk of breast cancer after 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95%CI	Additional cases per 1000 HRT users over 5 years (95%CI)
		CEE oestrogen-only	
50-79	21	0.8 (0.7 – 1.0)	-4 (-6 – 0)*
		CEE+MPA oestrogen & progestagen‡	
50-79	17	1.2 (1.0 – 1.5)	+4 (0 – 9)

‡When the analysis was restricted to women who had not used HRT prior to the study there was no increased risk apparent during the first 5 years of treatment: after 5 years the risk was higher than in non-users.
* WHI study in women with no uterus, which did not show an increase in risk of breast cancer.

Endometrial cancer risk

Postmenopausal women with a uterus
The endometrial cancer risk is about 5 in every 1000 women with a uterus not using HRT.

In women with a uterus, use of oestrogen-only HRT is not recommended because it increases the risk of endometrial cancer (see section 4.4).

Depending on the duration of oestrogen-only use and oestrogen dose, the increase in risk of endometrial cancer in epidemiology studies varied from between 5 and 55 extra cases diagnosed in every 1000 women between the ages of 50 and 65.

Adding a progestagen to oestrogen-only therapy for at least 12 days per cycle can prevent this increased risk. In the Million Women Study the use of five years of combined (sequential or continuous) HRT did not increase risk of endometrial cancer (RR of 1.0 (0.8-1.2)).

Ovarian cancer

Use of oestrogen-only or combined oestrogen-progestagen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see Section 4.4).

A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using HRT compared to women who have never used HRT (RR 1.43, 95% CI 1.31-1.56). For women aged 50 to 54 years taking 5 years of HRT, this results in about 1 extra case per 2000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2000 will be diagnosed with ovarian cancer over a 5-year period.

Risk of venous thromboembolism

HRT is associated with a 1.3-3-fold increased relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of using HRT (see section 4.4). Results of the WHI studies are presented:

WHI Studies - Additional risk of VTE over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95%CI	Additional cases per 1000 HRT users
Oral oestrogen-only*			
50-59	7	1.2 (0.6-2.4)	1 (-3 – 10)
Oral combined oestrogen-progestagen			
50-59	4	2.3 (1.2 – 4.3)	5 (1 - 13)

* Study in women with no uterus.

Risk of coronary artery disease

- The risk of coronary artery disease is slightly increased in users of combined oestrogen-progestagen HRT over the age of 60 (see section 4.4).

Risk of ischaemic stroke

- The use of oestrogen-only and oestrogen + progestagen therapy is associated with an up to 1.5-fold increased relative risk of ischaemic stroke. The risk of haemorrhagic stroke is not increased during use of HRT.
- This relative risk is not dependent on age or on duration of use, but as the baseline risk is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age, see section 4.4.

WHI studies combined - Additional risk of ischaemic stroke* over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95%CI	Additional cases per 1000 HRT users over 5 years
50-59	8	1.3 (1.1 - 1.6)	3 (1-5)

* No differentiation was made between ischaemic and haemorrhagic stroke

Other adverse reactions have been reported in association with oestrogen/progestagen treatment:

- Gall bladder disease.
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura.
- Probable dementia over the age of 65 (see section 4.4).
- Dry eyes.
- Tear film composition changes.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [to be completed nationally].

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 progestagen 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 administered 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 toxicity profiles of estradiol and norethisterone have been well established. Long-term, continuous administration of natural and synthetic oestrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver. Long-term, continuous administration

of norethisterone in certain animal species increases the frequency of tumours of the hypophysis and ovary in females, and of liver and breast in males.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Phase I

Adhesive matrix:
acrylic and silicone adhesive matrix
oleyl alcohol
dipropylene glycol
povidone (E1201)

Backing layer:
ethylene/vinyl acetate copolymer and vinylidene chloride/methyl acrylate copolymer laminate

Release liner:
fluoropolymer-coated polyester film

Phase II

Adhesive matrix:
acrylic and silicone adhesive matrix
povidone (E1201)
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 **18 months; 17 months** stored in a refrigerator (2-8ºC) plus 1 month 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

Used transdermal patches should be folded in half with the adhesive side inwards, and discarded safely and out of the reach and sight of children. Any used or unused transdermal patches should be disposed of in accordance with local requirements or returned to the pharmacy, preferably in the original packaging.

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<Date of first authorisation: {DD month YYYY}>
<Date of last renewal: {DD month YYYY}>
<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

2025-07-17