Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

AERODIOL 150 micrograms/dose, nasal spray solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each spray delivers 0.07 ml of solution which contains estradiol equivalent to 150 micrograms of estradiol hemihydrate.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Nasal spray, solution

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hormone replacement therapy (HRT) for oestrogen deficiency symptoms in post menopausal women.
The experience of treating women older than 65 years is limited.

4.2 Posology and method of administration

NASAL ROUTE.
The recommended dose for initiation of treatment is 150 micrograms (1 spray) in a nostril.
After 2 or 3 cycles the dosage may be adjusted in response to clinical symptoms:
The usual maintenance dose is 300 micrograms (2 sprays) per 24 hours, i.e. 1 spray in each nostril once daily.

- If symptoms of oestrogen deficiency persist, the number of sprays may be increased up to 3 or 4 per day (450 micrograms or 600 micrograms), in divided doses, morning and evening.
- In the event of signs of hyperoestrogenism such as breast tenderness, abdominal bloating, anxiety, nervousness or aggressiveness, the dosage should be reduced to 1 spray (150micrograms) daily.

For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration (see also section 4.4 "Special warnings and special precautions for use") should be used.

AERODIOL may be administered as cyclic or continuous treatment:

- Cyclic treatment: AERODIOL is used cyclically for a duration of 21 to 28 days, followed by a 2- to 7-day treatment-free period.
- Continuous treatment: AERODIOL is administered daily without a break in treatment. Continuous (non-cyclic) treatment may be indicated in hysterectomised women and in cases where oestrogen deficiency symptoms occur during the treatment-free period.

For non-hysterectomised women, AERODIOL is recommended to be combined with progestogen treatment for at least 12 days per cycle to avoid oestrogen-induced endometrial hyperplasia. (see section 4.4 "Special warnings and special precautions for use").

Sequential progestogen treatment should be administered as follows:

- If AERODIOL is administered cyclically, a progestogen will be added to estradiol for at least the last 12 days of treatment. Thus, no hormones will be administered during the treatment-free period of the cycle.

- If AERODIOL is administered continuously, it is recommended to take a progestogen for at least 12 days each month.

In either case, withdrawal bleeding will usually occur when the progestogen is discontinued.

Unless there is a previous diagnosis of endometriosis, it is not recommended to add a progestogen in hysterectomised women.

Patients changing from another cyclic or continuous sequential preparation should complete the cycle and may then change to AERODIOL without a break in therapy. Patients changing from a continuous combined preparation may start therapy at any time.
Priming: before it is first used, the bottle must be primed by firmly activating the pump 3 times.
The bottle should be held vertically during administration. The head is bent slightly forward and the nozzle introduced into each nostril in turn. Pressure is then exerted on the pump. The patient must not breathe in during spraying nor blow the nose immediately afterwards.

In the event of a severely blocked nose, AERODIOL may be administered temporarily via the oromucosal route by administration via the upper gingival sulcus. In such circumstances, the usual dosage should be doubled.
Patients with a runny nose should blow their nose before administration of AERODIOL.

Dosing should preferably take place at the same time every day.
If a dose is forgotten, it can be given at any time up to the next scheduled dose but it should not be doubled. Forgetting a dose may increase the likelihood of breakthrough bleeding and spotting.

The risk/benefit ratio should be re-evaluated regularly to adjust the treatment if needed:
- For the duration of treatment with AERODIOL.
- When changing from another hormonal treatment to AERODIOL.

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 estradiol hemihydrate or to any of the excipients.
- 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

<u>Medical examination/follow up</u>
- 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 contraindications and warnings 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. Investigations, including mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

<u>Conditions which need supervision</u>
- 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 Aerodiol, 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.* first 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.
- A history of endometrial hyperplasia (see below).
- Epilepsy.
- Asthma.
- Otosclerosis.
- Recurrent epistaxis.

Reasons for immediate withdrawal of therapy:
Therapy should be discontinued if 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 progestogen for at least 12 days per cycle in non-hysterectomised women greatly reduces this risk. For doses of 450 micrograms/d and 600 micrograms/d, the endometrial safety of added gestagens has not been studied.
- 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. Such investigations may include endometrial biopsy to exclude endometrial malignancy. Unopposed oestrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore, the addition of progestogens to oestrogen replacement therapy should be considered in women who have undergone hysterectomy because of endometriosis, especially if they are known to have residual endometriosis.

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 or oestrogen-progestogen combinations or tibolone for HRT for several years (see section 4.8 "Undesirable effects"). 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 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 oestrogen 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 1,000 women aged 50-59 years and 8 per 1,000 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 (Body Mass Index > 30kg/m²) and systemic lupus erythematosus (SLE). There is no consensus about the 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 HRT.
- The risk of VTE may be temporarily increased with prolonged immobilisation, major trauma or major surgery. As in all post-operative 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 four to six 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 doctors immediately if 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 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 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 5-10 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 patients with cardiac or renal dysfunction should be carefully observed. Patients with terminal renal insufficiency should be closely observed, since it is expected that the levels of circulating oestrogens from AERODIOL 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 oestrogen therapy in this condition.

- Estrogens 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 post-menopausal women or other HRT products.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations requiring precautions for use:

- Enzyme inducers:

The metabolism of oestrogens 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).

After nasal administration, the first-pass effect in the liver is avoided and, therefore, nasally administered oestrogens such as AERODIOL might be less affected by enzyme inducers than orally administered hormones.

- Antiretroviral agents:

Ritonavir and nelfinavir, although known as strong enzyme inhibitors, by contrast exhibit enzyme inducing properties when used concomitantly with steroid hormones.
Herbal preparations containing St John's Wort (*Hypericum perforatum*) may induce the metabolism of oestrogens.
Clinically, an increased metabolism of oestrogens and progestogens may lead to a decreased effect and changes in the uterine bleeding profile.

- Nasal corticosteroids and nasally administered vasoconstricting agents:

The effect of concomitant administration of nasal corticosteroids or nasal vasoconstricting agents has not been studied.
AERODIOL should not be administered immediately after nasal corticosteroids or nasal vasoconstricting agents.

4.6 Pregnancy and lactation

Pregnancy:
AERODIOL is not indicated during pregnancy. If pregnancy occurs during medication with AERODIOL treatment should be withdrawn immediately.
The results to date of most epidemiological studies relevant to inadvertent foetal exposure to oestrogens indicate no teratogenic or foetotoxic effects.

Lactation:
AERODIOL is not indicated during lactation.

4.7 Effects on ability to drive and use machines

No effects on ability to drive or use machines have been observed.

4.8 Undesirable effects

The most frequently reported undesirable effects (>10%) during treatment with AERODIOL are symptoms at the application site: prickling-tingling sensation, sneezing and rhinorrhoea.

Other undesirable effects reported in users of AERODIOL or other non-oral estradiol preparations are listed in the table.

Organ system	Common ADRs >1/100, <1/10	Uncommon ADRs >1/1000, <1/100	Rare ADRs >1/10.000, <1/1000
Body as a whole	Headache,	Fluid retention/oedema, weight increase/loss, dizziness, fatigue, leg cramps, migraine	
Gastrointestinal	Nausea	Bloating, abdominal cramps	Cholelithiasis, cholestatic jaundice
Reproductive	Breakthrough bleeding, spotting, mastodynia	Dysmenorrhoea, endometrial hyperplasia, benign breast tumours,	Increase in size of uterine fibroids
Respiratory tract	Epistaxis		
Skin and appendages		Acne, pruritus	Urticaria
Cardiovascular		Hypertension	
Psychiatric	Increase/decrease in libido		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 "Special warnings and special precautions for use").

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 treatment:
- 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 HRT users than among non-users. For further information, see sections 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 "Special warnings and special precautions for use").

4.9 Overdose

The route of administration makes significant acute overdose unlikely. The effects of overdose are generally breast tenderness, abdominal/pelvic bloating, nausea and aggressiveness.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Classification: G03CA03.
OESTROGENS (Genitourinary system and sex hormones).
The active ingredient, synthetic 17 beta-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. AERODIOL constitutes pulsed oestrogen therapy that provides a hormone exposure similar to that found during the early to mid follicular phases of the menstrual cycle.

During treatment, due to the mechanism of action, the minimum FSH values are observed 6 to 8 hours post-dosing and a decrease is still present immediately before the next dose.

Relief of menopausal symptoms was achieved during the first few weeks of treatment with AERODIOL.

5.2 Pharmacokinetic properties

When administered at a dose of 300 micrograms AERODIOL achieves peak serum estradiol levels around 1000 pg/mL, 10 to 30 minutes post-dosing. 17 beta-estradiol (E_2) is rapidly distributed. Return to values close to baseline occurs within 12 hours of dosing.
The absolute bioavailability of estradiol when administered by the nasal route is around 25% and is higher than that following oral administration because AERODIOL avoids intestinal and liver first pass effects in contrast to orally administered oestrogens.
Hormone exposure, as expressed by the area under the curve of plasma estradiol concentration against time (AUC_{24h}) is proportional to the dose. Following nasal administration of 300 micrograms, the AUC_{24h} is similar to that obtained using other administration routes (patch delivering 50 micrograms/d, 2-mg tablet) but with a different kinetic profile (pulse).
In clinical trials, no case of non-absorption was observed.
E_1 (Estrone)/E_2 ratios are around 1. A 20% decrease in bioavailability of estradiol has been observed in heavy smokers (1 pack/day).
Cigarette smoking immediately before AERODIOL administration does not modify the nasal absorption of estradiol.

5.3 Preclinical safety data

Local tolerability studies in animals have shown that nasal administration of estradiol does not damage the nasal mucosa.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methyl beta-cyclodextrin (RAMEB)
Sodium chloride
Sodium hydroxide or hydrochloric acid
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

4.2 ml (60 sprays) in a bottle (Type-1 glass) with a metering pump (polypropylene) and a nasal applicator (polypropylene); packs of 1 and 3 bottles.

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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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