Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Naemis Tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Pink tablet:
Each pink tablet contains 1.5 mg estradiol (as 1.55 mg estradiol hemihydrate)
Excipient: lactose monohydrate (135.745 mg) and cochineal red A (E124), aluminium lake.

White tablet:
Each white tablet contains 1.5 mg estradiol (as 1.55 mg estradiol hemihydrate) and 3.75 mg nomegestrol acetate
Excipient: lactose monohydrate (130.175 mg).

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

Round pink tablet and round white tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hormone replacement therapy (HRT) for oestrogen deficiency symptoms in post-menopausal women.

4.2 Posology and method of administration

Oral route

NAEMIS is a cyclic combination of oestrogen and progestogen.

The therapeutic scheme is as follows :

One tablet per day for 24 consecutive days in the following order :
- From day 1 to 10, one pink tablet (Estradiol)
- From day 11 to 24, one white tablet (Estradiol combined with Nomegestrol acetate).

After a treatment-free interval of 4 days, the next sequence is to be taken in the same way, even if withdrawal bleeding has not stopped.

In women who have never taken HRT or who are switching from combined continuous HRT, NAEMIS can be started on any day of the cycle.

However, if the patient is currently taking sequential HRT, the current treatment cycle must be completed before starting treatment with NAEMIS.

If a dose is forgotten, the treatment must be taken again as prescribed (a double dose must not compensate for the single dose that has been forgotten). Forgetting a dose may increase the likelihood of intercurrent bleeding or spotting.

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.

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),
- 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;
- 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 maw level of absolute risk in younger women, however, the balance of benefits and risks for these women may be more favourable the 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 contra-indications 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 (see 'Breast cancer' below).

Investigations, including 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 NAEMIS, in particular:

- Leiomyoma (uterine fibroids) or endometriosis;
- History of, or risk factors for, thromboembolic disorders (see below)
- Risk factors for estrogen 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
- A history of endometrial hyperplasia (see below)
- Epilepsy
- Asthma
- Otosclerosis

Reasons for immediate withdrawal of therapy
Therapy should be discontinued in case a contra-indication is discovered and in the following situations:
- o Jaundice or deterioration in the liver function
- o Significant increase in blood pressure
- o New onset of migraine-type headache
- o Pregnancy

Endometrial hyperplasia and carcinoma
- o In women with an intact uterus, the risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administrated 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.
- o The addition of a progestagen cyclically for at least 12 days per months/28 day cycle or continuous combinated oestrogen-progestagen therapy in non-hysterectomised women prevents the excess risk associated with oestrogen-only HRT.
- o 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 suggests an increased risk of breast cancer in hysterectomised women using oestrogen-progestagen and possibly also oestrogen-only HRT, that is dependent on the duration of taking HRT.

The randomised placebo-controlled trial the *Women's Health Initiative Study* (WHI) and epidemiological studies are consistent in finding and increased risk of breast cancer in women taking combined oestrogen-progestagen for HRT that becomes apparent after about 3 years (Cf. section 4.8).

The excess risk becomes apparent within a few years of use but return to baseline within a few (at most five) years after stopping treatment.

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

Ovarian cancer
Ovarian cancer is much rarer than breast cancer. Long term (at least 5-10 years) use of oestrogen-only HRT products has been associated with a slightly increased of ovarian cancer (see section 4.8). Some studies including the WHI trail suggest that the long term use of combined HRTs may confer similar, or slightly smaller risk (see section 4.8).

Venous thromboembolism

- o 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).
- o Patients with known trombophibic states and increased risk of VTE and HRT may add to this risk. HRT is therefore contraindicated in these patients (see section 4.3).
- o Generally recognised risk factors for VTE include, use of oestrogens, older age, major surgery, prolongated immobilisation, obesity (BMI > 30 kg/m2), pregnancy/postpartum period, systemic lupus erythematosus (SLE) and cancer. There is no consensus about the possible role of varicose veins in VTE.

- o 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 for 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilised.
- o 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 counseling regarding its limitations (only a proportion of thrombophilic defects are identified by screening).

If a thrombophilic defect is identified which segragates 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.

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

o 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 protectino against myocardial infarction in women with of without existing CAD who received combined oestrogen-progestagen or oestrogen-only HRT. The relative risk of CAD during use of combinated oestrogen+progestagen HRT is slightly increased. As the baseline absolute risk of CAD is 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. 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 in 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).

Other conditions:
o Oestrogens may cause fluid retention and therefore patients with cardiac or renal dysfunction should be carefully observed.
o Women with pre-existing familial hypertriglyceridemia should be followed closely during hormone replacement therapy since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oestrogen therapy in this condition.
o 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 (measured by radioimmunoassay). T3 resin uptake is decreased, reflecting the rise in TBG. Free T4 and free T3 concentrations are unchanged. Other binding proteins may be elevated in serum, i.e. corticoid binding globulin (CBG), sex-hormone-binding globulin (SHBG) leading to a rise in the circulating levels of 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).
o 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.

Due to the presence of lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose- galactose malabsorption should not take this medicine The presence of cochineal red (E124), may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of oestrogens and progestogens may be increased by concomitant use of enzyme-inducer medication, particularly iso-enzymes from cytochrome P450 enzymes, such as anticonvulsives (e.g. phenobarbital, phenytoin, carbamazepin) and anti-infectious agents (e.g. rifampicin, rifabutin, nevirapine, efavirenz).

Taking rifampicin simultaneously decreases the bioavailability of Nomegestrol acetate by 91% and increases that of Estradiol by 28 %.
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.

Clinically, an increased metabolism of oestrogens and progestagens may lead to a decrease in the therapeutic effect and changes in uterine bleeding profile.

4.6 Fertility, pregnancy and lactation

Pregnancy
NAEMIS is not indicated during pregnancy.

If pregnancy occurs during medication with NAEMIS, treatment should be withdrawn immediately.
Clinically, data on limited number of exposed pregnancies indicate no adverse effects of nomegestrol acetate on the foetus.

The results of most epidemiological studies to date relevant to inadvertent foetal exposure to combination of oestrogens + progestagens indicate no teratogenic or foetotoxic effect.

Lactation
NAEMIS is not indicated during lactation.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

During Phase III and IV clinical trials, the very common (≥ 10%) undesirable effects encountered were mastodynia, spotting and intercurrent bleeding. These effects are usually observed during hormone treatment of the menopause. The adverse drug reactions in attached table are those found in phase III clinical trials of NAEMIS appearing in less than 10% of cases:

System	Common undesirable effects (≥ 1% - < 10%)	Uncommon undesirable effects (≥ 0.1 % - < 1%)
Reproductive system and breast disorders	Dysmenorrhea, menorrhagia, menstrual disorders, leucorrhea, aggravation of uterine fibroids, pelvic pain	Benign breast tumour, uterine polyp, endometriosis, vaginal candidosis, increase in breast volume
Gastro-intestinal disorders	Abdominal pain or swelling	Vomiting, constipation, diarrhoea
Nervous system disorders	Headaches	Migraine, dizziness

Musculoskeletal, connective tissue and bone disorders	Muscular cramps, limb pain	Arthralgia
Psychiatric disorders	Nervousness, depression	
Vascular disorders		Superficial or deep venous thrombosis, thrombophlebitis, arterial hypertension,
General disorders	Weight gain	Peripheral oedema, asthenia, increased appetite
Skin and subcutaneous tissue disorders		Cutaneous rash, pruritus, alopecia
Hepato-biliary disorders		Abnormal hepatic values

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.
- Any increased risk in users of oestrogen-only therapy is substantially lower than that seen in users of oestrogen-progestagen combinations.
- The level of risk is dependent on the duration (see section 4.4).
- Results of the largest randomized placebo-controlled trial (WHI-study) and largest epidemiological study (MWS) are presented.

Million Women study– Estimated additional risk of breast cancer after 5 years' use

Age range (years)	Additional cases per 1000 never-users of HRT over a 5 year-period*2	Risk ratio & 95%CI#	Additional cases per 1000 HRT users over 5 years (95%CI)
Oestrogen only HRT			
50-65	9-12	1.2	1-2 (0-3)
Combined oestrogen-progestagen			
50-65	9-12	1.7	6 (5-7)
#Overall risk ratio. The risk ratio is not constant but will increase with increasing duration on use 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 (yrs)	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)*3
CEE+MPA oestrogen & progestagen‡			
50-79	14	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.

*2 *Taken from baseline incidence rates in developed countries*
*3 *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 an 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

Long-term use of oestrogen-only and combined oestrogen-progestagen HRT has been associated with a slightly increased risk of ovarian cancer. In the Million Women Study 5 years of HRT resulted in 1 extra case per 2500 users.

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 HT (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*4			
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)

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*5 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)

*4 *Study in women with no uterus*
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).

4.9 Overdose

An overdose manifests itself through tightness in the breast, abdomino-pelvic swelling, irritability, nausea, vomiting and/or metrorrhagia. There is no antidote but treatment for the symptoms may be given.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

PROGESTOGENS AND OESTROGENS FOR SEQUENTIAL ADMINISTRATION.

ATC Code: G03FB (genito-unrinary system and sex hormones)

NAEMIS is a non-contraceptive cyclic oestroprogestogen combination containing estradiol and Nomegestrol acetate.

Estradiol: the active substance 17-β 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.

Nomegestrol acetate: Nomegestrol acetate is a synthetic progestogen derived from 19-norprogesterone. It has no androgenic and oestrogenic activity and the affinity of Nomegestrol acetate with the progesterone receptor is 2.5 times that of the natural hormone.

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

The adding of Nomegestrol acetate, in the second part of the treatment, induces withdrawal bleeding.

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

Regular withdrawal bleeding occurred in 93 % of cycles with a mean duration of 4.7 days.

Withdrawal bleeding usually started 4 days after the last pill of the progestagen phase.

Break through bleeding and /or spotting appeared in 12.7% of the women during the first three months of therapy and in 10.6 % during the last three months of treatment. Amenorrhea (no bleeding or spotting) occurred in 0.6 % of the women during the first year of treatment.

5.2 Pharmacokinetic properties

The association of 17-β Estradiol and Nomegestrol acetate does not clinically modify in a significant way the bioavailability of either of the active substances taken in isolation.
The administration and association of 17-β plus Estradiol and Nomegestrol acetate brings about an increase of 25 % of the maximum concentration for Estradiol and 36 % for Nomegestrol compared to separate administration of the 2 products. The absorption is quick with an observed Tmax of about 1 hour for Estradiol and 2 hours for Nomegestrol acetate.
The pharmacokinetic profile of Estradiol and Nomegestrol acetate in its steady state is as follows:
Estradiol:
Minimum concentration (Cmin) 43 (± 4.8) pg/ml
Maximum concentration (Cmax) 290 (± 32.7) pg/ml
Mean concentration (Cmean) 72 (± 5.6) pg/ml
Total area under the curve 2765 (± 270.0) pg.h/ml
Nomegestrol acetate:
Minimum concentration (Cmin) 6.5 (± 0.40) ng/ml
Maximum (Cmax) 20.4 (± 1.00) ng/ml
Mean concentration (Cmean) 8.6 (± 0.40) ng/ml
Total area under the curve 630.3 (± 41.64) ng.h/ml

5.3 Preclinical safety data

Animal studies with estradiol, nomegestrol acetate or combination have indicated expected estrogenic and gestagen effects. Reproductive toxicity, genotoxicity or carcinogenicity studies were not conducted with the combination estradiol : nomegestrol acetate.Estradiol displayed embryofetal effects at relatively low doses. Nomegestrol acetate was not genotoxic nor teratogenic.
There are no additional preclinical data relevant to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pink tablet:
Povidone (K25 or K30),
Lactose monohydrate,
Microcrystalline cellulose,
Glycerol distearate,
Silica colloidal anhydrous,
Crospovidone,
Cochineal red A (E124), aluminium lake.

White tablet:
Povidone (K25 or K30),
Lactose monohydrate,
Microcrystalline cellulose,
Glycerol distearate,
Silica colloidal anhydrous,
Crospovidone.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Do not store above +25°C.

Store in the original package in order to protect from humidity.

6.5 Nature and contents of container

Each blister (PVC/PE/ACLAR/Aluminium) contains 10 pink tablets and 14 white tablets.
Box of 1 and 3.
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

Naemis tablets no longer required should not be disposed via wastewater or the municipal drainage system. The hormonal active compounds in the tablet may have harmful effects if reaching the aquatic environment. Return them to a pharmacy or dispose them in another safe way according to local requirements. These measures will help to protect the environment.

7 MARKETING AUTHORISATION HOLDER

Merck Serono Ltd
Bedfont Cross
Stanwell Road
Feltham
Middlesex
TW14 8NX
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8 MARKETING AUTHORISATION NUMBER

PA 654/14/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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