

Natragen® Cream 0.2% w/w Cream

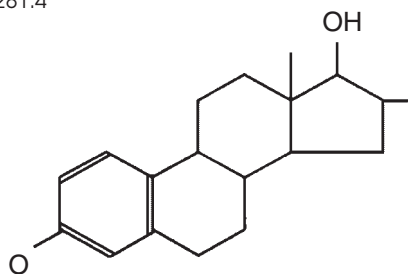
Product Information

Composition Active: Oestradiol (as oestradiol hemihydrate B.P.)

Chemical Name: Estra-1,3,5,(10)-triene -3, 17β-diol (as hemihydrate)

Molecular Weight: 281.4

CAS: 35380-71-3



Oestradiol
C₁₈H₂₄O₂

.1/2 H₂O

Description:

Natragen® contains the active ingredient oestradiol hemihydrate (micronised) in a white vanishing - cream base.

Contains dl-α tocopherol acetate (Vitamin E), macadamia nut oil and almond oil.

Pharmacology

Oestradiol is a naturally occurring oestrogenic hormone. Oestradiol is formed from steroid precursors in the ovarian follicles of premenopausal women, under the influence of the pituitary. In men and postmenopausal women oestrogens are formed in the adipose tissue of the adrenal glands and other organs; in pregnancy large amounts are produced by the placenta. Oestradiol is responsible for development and maintenance of the female sex organs, secondary sex characteristics and mammary glands. Functioning of aspects of the uterus and accessory organs, particularly the proliferation of the endometrium and cyclical changes to the cervix and vagina are under the influence of oestradiol. Progesterone complements the action of oestradiol for the complete biological function of the sex organs.

Oestradiol is absorbed from the gastro-intestinal tract, through the skin and mucus membranes. When taken orally oestradiol is transported via plasma proteins once absorbed oestradiol undergoes some enterohepatic recycling and is rapidly metabolised by the liver to the less active oestrinol and oestrone. It is excreted in the urine as glucuronide and sulphate esters together with a small percentage unchanged and also other metabolites.

Pharmacokinetics

Natragen® is an oil-in-water based oestradiol cream. After application oestradiol is absorbed through the skin into the circulation. There is a degree of oestradiol absorbed in the subcutaneous tissue and slow residual release into the circulation. Transdermal application avoids the hepatic first-pass effect encountered with oral dose forms of oestrogens.

Variable oestradiol plasma concentrations can be encountered with individual, but generally a steady-state bioavailability with Natragen® is achieved after 2 weeks continual daily usage.

Indications

Natragen® is indicated for the management of climacteric symptoms after natural or surgical menopause. Symptoms of the climacteric include hot flushes, night sweats, vaginal dryness, moods changes, memory loss, and fatigue.

In women with an intact uterus, oestrogen should always be opposed by progestagen in an adequate dosage regimen to ensure secretory transformation of the endometrium at regular intervals. Hysterectomised women who require postmenopausal hormone therapy should receive oestrogen only hormone therapy unless otherwise indicated.

Clinical Trials

In light of the findings of a large-scale prospective, randomised clinical trial, the Women's Health Initiative (WHI) (1) involving 8,506 postmenopausal women, examining the use of oral hormone replacement therapy (HRT) using a continuous combined regimen of conjugated equine oestrogens (conjugated oestrogens) 0.625mg/day plus medroxyprogesterone acetate 2.5mg/day it is recommended that combined hormone replacement therapy not be used for the long-term maintenance of good health, including

the prevention of cardiovascular disease. In the absence of data specific to this product it is recommended that prior to prescribing consideration must be given to the potential for cardiovascular, thrombotic and neoplastic adverse events.

A second study, The Million Women's Study, an observational study of 1,084,110 women, of whom 828,923 were postmenopausal, has shown that, compared to never users, use of oestrogen/progestagen combined HRT is associated with a higher risk of breast cancer than use of oestrogens alone. Results including relative risks are outlined under Precautions.

Contraindications:

Natragen® is contraindicated in patients with

- family and personal history of carcinoma of the breast or endometrium
- Endometriosis
- Undiagnosed vaginal bleeding
- Previous thrombo-embolic disorder
- Cardiovascular disease
- Thrombophlebitis
- Herpes gestationis
- Liver impairment
- Pregnancy and lactation
- Non-hysterectomised women unless on concomitant progestogen therapy
- Know hypersensitivity to Natragen® or any of its components

Precautions:

HRT should not be initiated or continued to prevent or treat cardiovascular disease.

The benefits and risks of HRT must always be carefully weighed, including consideration of the emergence of risks as therapy continues. HRT should be used only in women with menopausal symptoms and ordinarily not for long term use.

Oestrogens with or without progestagens should be prescribed at the lowest effective doses and for the shortest duration consistent with the treatment goals and risks for the individual women. The risks of HRT should be assumed to be similar for all doses of oestrogens and oestrogens/progestagen combinations.

Information from Clinical Trials: Million Women Study. The results of the study were based on the follow up of one million, eighty-four thousand, one hundred and ten (1,084,110) women. The average age of the women at recruitment was 55.9 years and the average period of follow up was 2.6 years for analyses of the cancer incidence and 4.1 years for analyses of mortality. Overall, 50% of the study population had used HRT at some point. There were nine thousand, three hundred and sixty four (9,364) newly diagnosed cases of invasive breast cancer and six hundred and thirty seven (637) deaths from breast cancers. The current users of HRT at recruitment were more likely to develop breast cancer and to die from it. Past users of HRT were not at an increased risk of newly diagnosed or fatal disease. The incidence was significantly increased for current users of preparations containing oestrogen only, oestrogen/progestagen and tibolone but the magnitude of the associated risk was greater for the combined treatment than for any other preparation.

| HRT use at baseline | Cases / population | Relative Risk (95% FCI)* |
|-----------------------|--------------------|--------------------------|
| All never users | 2894/ 392 757 | 1.00 (0.96 – 1.04) |
| All past users | 1004/ 150179 | 1.01 (0.95 – 1.08) |
| Current users of: | | |
| Oestrogen only | 991/ 115 383 | 1.30 (1.22 – 1.38) |
| Oestrogen-progestagen | 1934/ 142 870 | 2.00 (1.91 – 2.09) |
| Tibolone | 184 / 18 186 | 1.45 (1.25 – 1.67) |
| Other/unknown types | 93 / 9548 | 1.44 (1.17 – 1.76) |

Relative risk of newly diagnosed invasive breast cancer in relation to recency and type of HRT used. FCI = floated CI. *Relative to never users, stratified by age, time since menopause, parity and age at first birth, family history of breast cancer, body-mass index, region and deprivation index. Modified from Lancet 2003 : 362 : 421.

An important finding of the Million Women Study was that the relative risk of breast cancer were increased separately from oral, transdermal and implanted oestrogen only formulations.

In terms of absolute risk, after ten years' use of HRT, it is estimated that there would be 5 (95% CI 3-7) additional breast cancers per 1,000 users of oestrogen only preparations and 19 (95% CI 15 – 23) additional cancers per 1,000 users of oestrogen/progestagen

combinations. The elevated risk reduces after discontinuation of hormone replacement therapy and is effectively lost after 5 years.

The Women's Health Initiative (WHI) enrolled a total of 27,000 predominantly healthy postmenopausal women to assess the risks and benefits of either long-term oestrogen replacement therapy (ERT) (conjugated oestrogens alone (0.625 mg/day) or hormone replacement therapy (HRT) (conjugated oestrogens in combination with medroxyprogesterone acetate (0.625 mg/2.5 mg/day)) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome studied. A global index included the first occurrence of the two primary outcomes plus stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture and death due to other causes. The study did not evaluate the effects of HRT on menopausal symptoms.

Results of the oestrogen plus progestagen study, which included 16,608 women (average age of 63 years, range 50 to 79) after an average follow-up of 5.2 years showed the relative risk of coronary heart disease was 1.29 (95% confidence interval 1.02 to 1.63), corresponding to an increase in the absolute rate from 30 to 37 per 10,000 woman years. The relative risk of stroke was 1.41 (1.07 to 1.85), an increase in the absolute rate from 21 to 29 per 10,000 woman years. The relative risk of venous thromboembolism (VTE) was 2.11 (1.58 to 2.82), an increase from 16 to 34 per 10,000 woman years. The relative risk of breast cancer was 1.26 (1.00 to 1.59), an increase from 30 to 38 per 10,000 woman years. The study was stopped prematurely because the preset criterion for invasive breast cancer was fulfilled and a global risk/benefit index supported the risks exceeding the benefits.

In a study of women aged 65 years of age and older (a randomised controlled sub-study of the Women's Health Initiative, the Women's Health Initiative memory study: n = 4,532, 54% older than 70), those treated with 0.0625 conjugated equine oestrogens + 2.5 mg medroxyprogesterone acetate were reported to have a two-fold increase in the risk of developing probable dementia. After an average follow up of 4 years the absolute risk of probable dementia was 45 per 10,000 women years in the oestrogen + progestagen group and 22 per 10,000 women years in the placebo group. It is unknown whether these findings apply to younger postmenopausal women. It is unlikely that HRT would be indicated in this age group.

Venous Thromboembolism (VTE)

Scarabin and others (3) reported the results of a case control study conducted during 1999-2002 in France. The investigators recruited 155 consecutive cases with a first documented episode of VTE of unknown cause (92 with pulmonary embolisms and 63 with deep venous thrombosis), and 381 controls (women admitted to hospital for other reasons) matched for centre, age, and time of recruitment. Overall, 32 (21%) cases and 27 (7%) controls were current users of oral oestrogen replacement therapy (this was defined in this study as oestrogen only therapy or combined HRT), whereas 30 (19%) cases and 93 (24%) controls were current users of transdermal oestrogen replacement therapy. After adjustment for potential confounding variables, the odds ratio for VTE in current users of oral and transdermal oestrogen replacement therapy compared with non-users was 3.5 (95% CI 1.8-6.8) and 0.9 (0.5-1.6), respectively.

Estimated risk for VTE in current users of oral oestrogen replacement therapy compared with transdermal oestrogen replacement therapy users was 4.0 (1.9-8.3).

These results may be interpreted as meaning that (i) the higher risk of VTE as shown in the WHI study has been further supported; and (ii) current use but not past use was a risk factor for VTE. Use in the first year was also more risky than later use, a finding that is also consistent with the WHI study.

Malignant Neoplasms

Breast Cancer

The use of oestrogens alone as well as combined/sequential oestrogen and progestagen use is associated with an increased risk of breast cancer. This emerges towards the end of the first year of treatment (see Million Women Study in Clinical Trials). Mortality can be increased in those who are diagnosed with incident breast cancers.

Mammographic density may be increased after the use of combined HRT. This may have implications for the sensitivity and specificity of breast cancer screening.

Combination HRT should not be used in hysterectomised women because it is not needed and it may increase the risk of breast cancer.

Epidemiological studies suggest that progestagen increases the risk of breast cancer compared to the use of oestrogens alone. Women should maintain a schedule of yearly breast examinations by healthcare provider, including mammography examinations and undertake regular self-examination.

Women with first-degree relatives who have had a history of breast cancer should be screened with mammography prior to initiation of therapy then at regular intervals. Regular breast examinations should be undertaken during treatment.

Other

Endometrial hyperplasia and uterine cancer are well documented adverse effects from unopposed oestrogen supplementation in women with an intact uterus. The addition of a cyclic progestagen in combination with Natragen® is essential for these women.

Natragen® is not recommended for patients with fibrocystic breast disease, ovarian cysts, endometrial hyperplasia or uterine fibroids.

Caution should be exercised when administering oestradiol to patients with heart failure, hypertension, reduced liver and kidney function, epilepsy or continual headache and migraine.

Natragen® contains almond oil and macadamia nut oil.

Caution is advised if the patient has an allergy or sensitivity to either of these ingredients.

Use in Pregnancy:

Oestrogens must not be used during pregnancy (Category B1)

Adverse Reactions:

In some patients oestrogens can cause side effects all of which are of variable severity. More commonly nausea, breast tenderness, bloating, abdominal pain, breakthrough bleeding, aggravated migraine and headache, weight gain, depression, fatigue and irritability have been reported. Less common effects include fluid retention, increased blood pressure, increased incidence of blood clotting, increased appetite and tinnitus.

Usual therapeutic dose:

Natragen® provides 1mg of oestradiol per 0.5g (1 unit) application. An applicator (with 1 unit graduations) is provided with each tube of Natragen®.

Usual starting dose is 1 unit (1mg oestradiol) applied once daily.

Natragen® is used either cyclically or continuously, in individually adjusted doses of 0.25g (half a unit) to 1g (2 units) per day, corresponding to 0.5 to 2mg oestradiol per day. Most patients start with 1mg oestradiol (1 unit) dose daily and adjustment can be made over 2 or 3 cycles.

Application should be made to either the lower trunk (abdomen) or upper thigh. The surface area of application should not exceed 200 sq. cms or approximately the area the size of the palm of two hands.

NOTE: Amount and duration of application must be tailored to individual requirements. Minimal dosing is optimal in patient management and wherever possible the lowest effective dose should be used.

It is recommended that duration of therapy in management of menopausal symptoms should be short term. After six months therapy the need for continued hormone therapy should be reconsidered.

Storage:

Store below 25C - DO NOT FREEZE.

POISONS SCHEDULE S4

Reference

1. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288(3):321-333.
2. Million Women Study Collaborators. *Lancet* 2003 362: 419 - 427.
3. Scarabin PY, Oger E at al *Lancet* 2003 362: 428 -432.

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