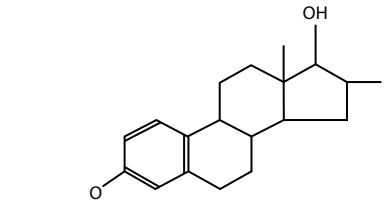
Natragen®

Cream containing 0.2% w/v (2mg/mL) Estradiol U.S.P. (Estra-1,3,5,(10)-triene –3, 17 β-diol)

PRODUCT INFORMATION

Composition Active: Estradiol U.S.P.
Chemical Name: Estra-1,3,5,(10)-triene –3, 17 β-diol
Molecular Weight: 272.4
CAS: 5864-38-0



Estradiol
$C_{18}H_{24}O_2$

Description

NATRAGEN® is a transdermal drug delivery system consisting of a white oil-in-water cream for topical administration of estradiol (micronized).

NATRAGEN® contains dl-α- tocopherol acetate (vitamin E), almond oil, cetomacrogol 1000, cetostearyl alcohol, butylated hydroxytoluene, citric acid, triethanolamine, Carbomer 940, B&J Phenonip® and water and is formulated to optimise systemic absorption of the active ingredient.

Pharmacology

Estradiol is a naturally occurring estrogenic hormone. Estradiol is formed from steroid precursors in the ovarian follicles of premenopausal women, under the influence of the pituitary. In men and postmenopausal women, estrogens are formed in the adipose tissue of the adrenal glands and other organs; in pregnancy large amounts are produced by the placenta. Estradiol 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 estradiol. Progesterone complements the action of estradiol for the complete biological function of the sex organs. Estradiol is absorbed from the gastro-intestinal tract, through the skin and mucus membranes. When taken orally estradiol is transported via plasma proteins. Once absorbed, estradiol undergoes some enterohepatic recycling and is rapidly metabolised by the liver to the less active estriol and estrone. It is excreted in the urine as glucuronide and sulphate esters together with a small percentage unchanged and also other metabolites.

Pharmacokinetics

After application of NATRAGEN® to the skin, estradiol is absorbed systemically via the subcutaneous tissue and slow residual release into the circulation. Transdermal application avoids the hepatic first-pass effect encountered with oral dose forms of estrogens.

Variable estradiol plasma concentrations can be encountered with most individuals; however, generally a steady-state bioavailability with NATRAGEN® is achieved after two weeks continual daily usage. Absorption is proportional to the surface area over which NATRAGEN® is applied. The surface area should be as small as possible and no greater than 200cm^2 (8 sq. inches).

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, estrogen should always be opposed by progestagen in an adequate dosage regimen to ensure secretory transformation of the endometrium at regular intervals. Hysterectomized women who require postmenopausal hormone therapy should not be excluded from using natural progesterone concurrently with estrogen therapy. The use of progesterone (PROFEME® 3.2% progesterone cream) in combination with NATRAGEN® will prevent adverse symptoms (estrogen dominance) due to the unopposed use of estrogen.

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
- Liver impairment
- Pregnancy and lactation
- Non-hysterectomised women unless on concomitant progestagen therapy
- Known hypersensitivity to NATRAGEN® or any of its components

Precautions

Hormone Therapy (HT) should not be initiated or continued to prevent or treat cardiovascular disease.

The benefits and risks of HT 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.

Estrogens 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 estrogens and estrogens/progestagen combinations.

Endometrial hyperplasia and uterine cancer are well documented adverse effects from unopposed estrogen 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 estradiol to patients with heart failure, hypertension, reduced liver and kidney function, epilepsy or continual headache and migraine.

PRODUCT INFORMATION (cont'd)

Precautions (cont'd)

Breast cancer: Estrogen therapy should never be used when there is active breast cancer. However the use of estrogen will not cause breast cancer. Caution is advised if estrogen is to be used in the long-term (> 5 years) and/or initiated in women older than 60 years because evidence shows that there is a higher risk of breast cancer incidence in these populations. Other risk factors include obesity, smoking and cardiovascular disease.

Thromboembolism and cardio-vascular risk: The HT-related risk for serious venous thromboembolic events increases with age (although minimal until age 60), and is also positively associated with obesity and thrombophilia. By avoiding first-pass hepatic metabolism, transdermal estrogen may avert the risk associated with oral HT. The impact on the risk of a thromboembolic event may also be affected by progestogen, depending on the type. Late starters of standard dose HT may have a transient slightly increased risk for coronary events. The risk of stroke is correlated with age. HT may increase the risk of stroke after the age of 60.[1]

Age: The safety of HT largely depends on age. Women younger than 60 years old should not be overly concerned about the safety profile of starting estrogen therapy. New data and re-analyses of older studies by women's age show that, for most women, the potential benefits of hormone therapy given for a clear indication are many and the risks are few when initiated within a few years of menopause.

NATRAGEN® contains almond oil. Caution is advised if the patient has an allergy or sensitivity to almond oil.

Use in Pregnancy

Estrogens must not be used during pregnancy (Category B1)

Adverse Reactions

In some patients estrogens 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

The recommended starting dose of NATRAGEN® is 0.5ml (1mg estradiol) applied once daily.

NATRAGEN® can be dose-titrated depending upon individual requirements up to a maximum of 2ml (4mg estradiol) daily.

NATRAGEN® provides 1mg of estradiol per 0.5ml via measured applicator.

Application should be made to either the lower trunk (abdomen) or upper thigh. The surface area of application should be kept to a minimum and should not exceed 200cm^2 (8 sq. inches) or approximately the area twice the size of the palm of the hand.

The patient should measure the appropriate dose using the applicator and apply directly to the skin massaging until absorbed. Directions for use of the applicator are contained within the box.

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.

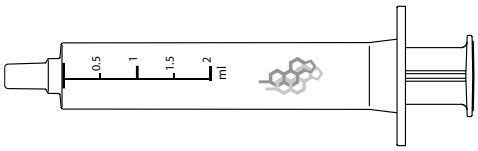
It is recommended that duration of therapy in management of menopausal symptoms should be short term. After six months therapy the need for continued hormone therapy should be reconsidered.

Presentation

NATRAGEN® 0.2% cream containing 2mg/mL estradiol U.S.P. in a 50ml boxed tube.

NATRAGEN® is supplied with a dose applicator marked with 0.5ml graduations. Each 0.5ml delivers a 1mg dose of estradiol.The patient should be directed to measure the appropriate unit dose using the graduated applicator and then apply to the skin.

Storage



Store below 25˚C - DO NOT FREEZE.
Shelf life under these conditions is 2 years.

Sponsor

HormoneSolutions.com
on behalf of Lawley Pharmaceuticals Pty Ltd
Unit 2/ 15A Harrogate Street, West Leederville, 6007
Western Australia, AUSTRALIA

Postal Address
P.O. Box 1146,
West Leederville, 6901
Western Australia, AUSTRALIA

International Telephone: +61 8 9388 0096
Fax: +61 8 9388 0098

USA & Canada Toll Free Phone: 1-800-961-7813
Toll Free Fax: 1-800-961-7650

Website: www.hormonesolutions.com
Email: info@hormonesolutions.com

NATRAGEN® 0.2% w/v estradiol cream 50ml

AUST L 169397

Date of Preparation: May 2011.

NATRAGEN® is a registered trademark.

References

1. Pines et al. IMS Updated Recommendations on postmenopausal hormone therapy CLIMACTERIC 2007;10:181–194