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Climara Pro (Estradiol, Levonorgestrel Transdermal)

??? ??????: 30 ??????/?????? 2017

The following serious adverse reactions are discussed elsewhere in the labeling:

- **WARNINGS AND PRECAUTIONS** ,**BOXED WARNING** Cardiovascular Disorders [see]
- **WARNINGS AND PRECAUTIONS** ,**BOXED WARNING** Malignant Neoplasms [see]

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below is from a one-year, prospective, multicenter, double blind, double dummy, randomized, controlled trial investigating the effect of three different dosage combinations of E2/LNG versus E2 alone on the development of endometrial hyperplasia. All women were postmenopausal, had a serum estradiol level of less than 20 pg/mL, and the sample included both symptomatic and asymptomatic women. The data below includes all adverse reactions reported at a frequency of > 3% in the E2/LNG 0.045 / 0.015 group (the approved dosage for Climara Pro, N=212) and the E2 alone group (N=204).

Table 1: All Treatment Emergent Reactions Regardless of Relationship Reported at a Frequency of > 3% with Climara Pro in the 1-year Endometrial Hyperplasia Study[a])

Body System Adverse Reaction	Climara Pro 0.045 / 0.015 N = 212	$_2$E N = 204
Body as a Whole		
Abdominal pain	9 (4.2)	11 (5.4)
Accidental injury	7 (3.3)	6 (2.9)
Back pain	13 (6.1)	12 (5.9)
Flu syndrome	10 (4.7)	13 (6.4)
Infection	7 (3.3)	10 (4.9)
Pain	11 (5.2)	13 (6.4)
Cardiovascular System		
Hypertension	7 (3.3)	9 (4.4)
Digestive System		
Flatulence	8 (3.8)	11 (5.4)
Metabolic and Nutritional		
Edema	8 (3.8)	5 (2.5)
Weight gain	6 (2.8)	10 (4.9)
Musculoskeletal System		
Arthralgia	9 (4.2)	10 (4.9)
Nervous System		
Depression	12 (5.7)	7 (3.4)
Headache	11 (5.2)	14 (6.9)
Respiratory System		
Bronchitis	9 (4.2)	7 (3.4)
Sinusitis	8 (3.8)	12 (5.9)
Upper respiratory infection	28 (13.2)	26 (12.7)
Skin and Appendages		
Application site reaction	86 (40.6)	69 (33.8)
Breast pain	40 (18.9)	20 (9.8)
Rash	5 (2.4)	10 (4.9)
Urogenital System		
Urinary Tract Infection	7 (3.3)	8 (3.9)
Vaginal Bleeding	78 (36.8)	44 (21.6)
Vaginitis	4 (1.9)	6 (2.9)

N = total number of subjects in a treatment group; n = number of [a] subjects with event.

Irritation potential of Climara Pro was assessed in a 3-week irritation study. The study compared the irritation of a Climara Pro placebo patch (22 cm^2) to a placebo (25 cm^2). Visual assessments of irritation were made on Day 7 of each wear period, approximately 30 minutes after patch removal using a 7-point scale (0 = no evidence of irritation; 1 = minimal erythema, barely perceptible; 2 = definite erythema, readily visible, or minimal edema, or minimal papular response; 3–7 = erythema and papules, edema, vesicles, strong extensive reaction).

The mean irritation scores were 0.13 (week 1), 0.12 (week 2), and 0.06 (week 3) for the Climara Pro placebo. The mean scores for the Climara placebo were 0.2 (week 1), 0.26 (week 2), 0.12 (week 3). There were no irritation scores greater than 2 at any timepoint in any subject.

In controlled clinical trials, withdrawals due to application site reactions occurred in 6 (2.1 percent) of subjects in the 12week symptom study and in 71 (8.5 percent) of subjects in the 1-year endometrial protection study.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of the Climara Pro transdermal system. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Genitourinary System

Changes in bleeding patterns

Gastrointestinal

Abdominal distension,* abdominal pain,* nausea

Skin

Alopecia, night sweats, pruritus,* Rash,* hot flush*

Central Nervous System

Dizziness, headache, insomnia

Miscellaneous

Application site reaction,* weight increased, anaphylactic reaction

* Combined two or more similar ARs