CLINICAL UPDATE

Brand Name	Lyllana™
Generic Name	estradiol
Drug Manufacturer	Amneal Pharmaceuticals LLC

Clinical Update

TYPE OF CLINICAL UPDATE

New Brand

FDA APPROVAL DATE

August 27, 2020

LAUNCH DATE

September 30, 2020

REVIEW DESIGNATION

STANDARD

TYPE OF REVIEW

Abbreviated New Drug Application (ANDA): 211396

DISPENSING RESTRICTIONS

Open

Overview

INDICATION(S) FOR USE

- Treatment of moderate to severe vasomotor symptoms due to menopause
- Prevention of postmenopausal osteoporosis

MECHANISMS OF ACTION

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue. Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (lh) and follicle stimulating hormone (fsh) through a negative feedback mechanism. Estrogens act to reduce the elevated concentrations of these hormones seen in postmenopausal women.

DOSAGE FORM(S) AND STRENGTH(S)

Transdermal system: 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day

DOSE & ADMINISTRATION

- For vasomotor symptoms: Start therapy with Lyllana™ 0.0375 mg per day applied to the skin twice weekly. Dosage adjustment should be guided by the clinical response.
- For postmenopausal osteoporosis prevention: Start therapy with Lyllana™ 0.025 mg per day applied to the skin twice weekly. The dose may be adjusted as necessary.

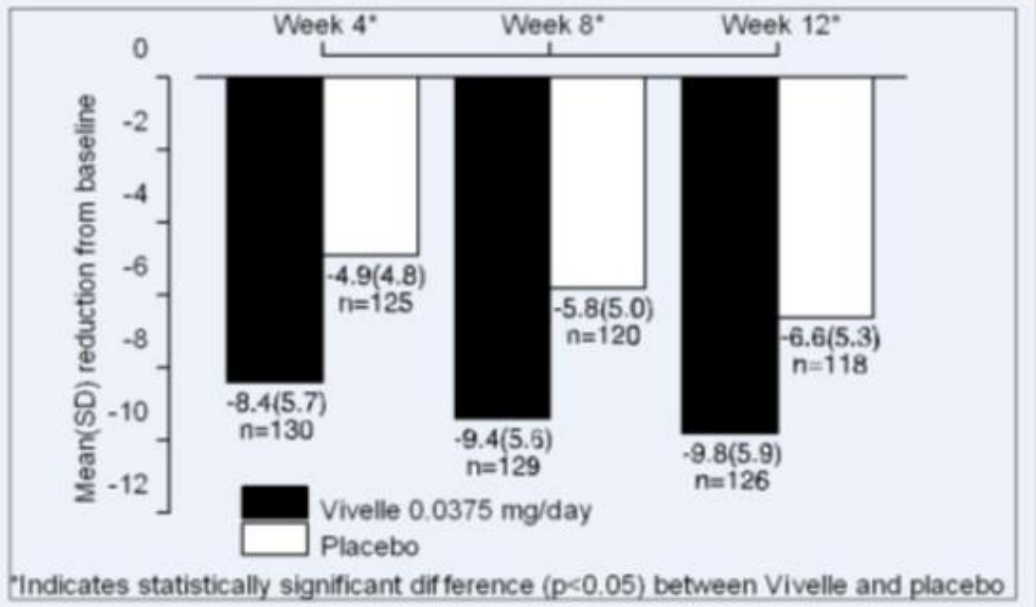
EFFICACY

Efficacy on Vasomotor Symptoms

There have been no efficacy and safety trials conducted with Lyllana™. In a pharmacokinetic study, Lyllana™ was shown to be bioequivalent to Vivelle.

In two controlled clinical trials with Vivelle, in a total of 356 subjects, the 0.075 and 0.1 mg doses were superior to placebo in relieving vasomotor symptoms at Weeks 4, 8 and 12 of treatment. In these studies, the 0.0375 and 0.05 mg doses did not differ from placebo at Week 4, therefore, a third 12-week placebo-controlled study in 255 subjects was performed with Vivelle to establish the efficacy of the lowest dose of 0.0375 mg. The baseline mean daily number of hot flushes in these 255 subjects was 11.5. Results at Weeks 4, 8, and 12 of treatment are shown in Figure 2.

Figure 2: Mean (SD) change from baseline in mean daily number of hot flushes for Vivelle 0.0375 mg versus Placebo in a 12-week trial.



The 0.0375 mg dose was superior to placebo in reducing both the frequency and severity of vasomotor symptoms at Weeks 4, 8 and 12 of treatment.

Efficacy on Bone Mineral Density

There have been no efficacy and safety trials conducted with Lyllana™. In a pharmacokinetic study, Lyllana™ was shown to be bioequivalent to Vivelle.

Efficacy and safety of Vivelle in the prevention of postmenopausal osteoporosis have been studied in a 2-year double-blind, randomized, placebo-controlled, parallel group study. A total of 261 hysterectomized (161) and non-hysterectomized (100), surgically or naturally menopausal women (within 5 years of menopause), with no evidence of osteoporosis (lumbar spine bone mineral density within 2 standard deviations of average peak bone mass, i.e., ≥0.0827 g/cm) were enrolled in this study; 194 patients were randomized to one of the four doses of Vivelle (0.1, 0.05, 0.0375, or 0.025 mg/day) and 67 patients to placebo. Over 2 years, study systems were applied to the buttock or the abdomen twice a week. Non-hysterectomized women received oral medroxyprogesterone acetate (2.5 mg/day) throughout the study.

There was an increase in BMD of the AP lumbar spine in all Vivelle dose groups; in contrast to this, a decrease in AP lumbar spine BMD was observed in placebo patients. All Vivelle doses were significantly superior to placebo ($p<0.05$) at all time points with the exception of Vivelle 0.05 mg/day at 6 months. The highest dose of Vivelle was

superior to the three lower doses. There were no statistically significant differences in pairwise comparisons among the three lower doses.