HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MINIVELLE safely and effectively. See full prescribing information for MINIVELLE.

MINIVELLE® (estradiol transdermal system)
Initial U.S. Approval: 1975

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER, and PROBABLE DEMENTIA
See full prescribing information for complete boxed warning.

Estrogen-Alone Therapy
- **There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens (5.2)**
- **Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia (5.1, 5.3)**
- **The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) (5.1)**
- **The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.3)**

Estrogen Plus Progestin Therapy
- **Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia (5.1, 5.3)**
- **The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke, and myocardial infarction (MI) (5.1)**
- **The WHI estrogen plus progestin substudy reported increased risks of invasive breast cancer (5.2)**
- **The WHIMS estrogen plus progestin ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.3)**

RECENT MAJOR CHANGES

Indications and Usage (1.2)	9/2014
Dosage and Administration (2.2)	9/2014
Warnings and Precautions (5.15)	9/2014

INDICATIONS AND USAGE

MINIVELLE® is an estrogen indicated for:
- Treatment of moderate to severe vasomotor symptoms due to menopause (1.1)
- Prevention of postmenopausal osteoporosis (1.2)

DOSAGE AND ADMINISTRATION

- For Vasomotor Symptoms: Start therapy with MINIVELLE® 0.0375 mg per day applied to the skin twice weekly. Dosage adjustment should be guided by the clinical response (2.1)
- For Postmenopausal Osteoporosis Prevention: Start therapy with MINIVELLE 0.025 mg per day applied to the skin twice weekly. The dose may be adjusted as necessary (2.2)
- MINIVELLE should be placed on a clean, dry area on the lower abdomen (below the umbilicus) or buttocks. MINIVELLE should not be applied to the breasts (2.3)

DOSAGE FORMS AND STRENGTHS

Transdermal system: 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day (3)

CONTRAINDICATIONS

- Undiagnosed abnormal genital bleeding (4)
- Known, suspected, or history of breast cancer (4, 5.2)
- Known or suspected estrogen-dependent neoplasia (4, 5.2)
- Active DVT, PE, or a history of these conditions (4, 5.1)
- Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions (4, 5.1)
- Known anaphylactic reaction or angioedema or hypersensitivity with MINIVELLE (4)
- Known liver impairment or disease (4, 5.10)
- Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders (4)
- Known or suspected pregnancy (4, 8.1)

WARNINGS AND PRECAUTIONS

- Estrogens increase the risk of gallbladder disease (5.4)
- Discontinue estrogen if severe hypercalcemia, loss of vision, severe hypertriglyceridemia or cholestatic jaundice occurs (5.5, 5.6, 5.9, 5.10)
- Monitor thyroid function in women on thyroid replacement therapy (5.11, 5.18)

ADVERSE REACTIONS

Most common adverse reactions (greater than or equal to 5 percent) with Vivelle are: headache, breast tenderness, back pain, pain in limb, and nasopharyngitis, dyspepsia, nausea, sinusitis, and intermenstrual bleeding (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Noven at 1-800-455-8070 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*

DRUG INTERACTIONS

Inducers and/or inhibitors of CYP3A4 may affect estrogen drug metabolism (7.1)

USE IN SPECIFIC POPULATIONS

- Nursing Mothers: Estrogen administration to nursing women has been shown to decrease the quantity and quality of breast milk. Detectable amounts of estrogens have been identified in the breast milk of women receiving estrogens. (8.3)
- Geriatric Use: An increased risk of probable dementia in women over 65 years of age was reported in the WHIMS ancillary studies of the WHI (5.3, 8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 9/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

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***Sections or subsections omitted from the full prescribing information are not listed.**

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FULL PRESCRIBING INFORMATION

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER, and PROBABLE DEMENTIA

Estrogen-Alone Therapy

Endometrial Cancer

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding *[see Warnings and Precautions (5.2)]*.

Cardiovascular Disorders and Probable Dementia

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.1, 5.3), and Clinical Studies (14.3, 14.4)]*.

The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg]-alone, relative to placebo *[see Warnings and Precautions (5.1), and Clinical Studies (14.3)]*.

The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions (5.3), Use in Specific Populations (8.5), and Clinical Studies (14.4)]*.

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.1, 5.3), and Clinical Studies (14.3, 14.4]*.

The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo *[see Warnings and*

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Precautions (5.1), and Clinical Studies (14.3)].

The WHIMS estrogen plus progestin ancillary study of the WHI, reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions (5.3), Use in Specific Populations (8.5), and Clinical Studies (14.4)].*

Breast Cancer

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer *[see Warnings and Precautions (5.2), and Clinical Studies (14.3)].*

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

1 INDICATIONS AND USAGE

1.1 Treatment of Moderate to Severe Vasomotor Symptoms Due to Menopause

MINIVELLE is indicated for the treatment of moderate to severe vasomotor symptoms due to menopause.

1.2 Prevention of Postmenopausal Osteoporosis

MINIVELLE is indicated for the prevention of postmenopausal osteoporosis.

Limitation of Use

When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.

2 DOSAGE AND ADMINISTRATION

Generally, when estrogen is prescribed for a postmenopausal woman with a uterus, a progestin should be considered to reduce the risk of endometrial cancer. A woman without a uterus does not need a progestin. In some cases, however, hysterectomized women with a history of endometriosis may need a progestin *[see Warnings and Precautions (5.2, 5.14)]*.

Use of estrogen-alone, or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman.

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Postmenopausal women should be re-evaluated periodically as clinically appropriate to determine if treatment is still necessary.

2.1 Treatment of Moderate to Severe Vasomotor Symptoms

Start therapy with MINIVELLE 0.0375 mg per day applied to the skin twice weekly. Dosage adjustment should be guided by the clinical response.

Therapy should be started at the lowest effective dose and the shortest duration consistent with the treatment goals. Attempts to taper or discontinue the medication should be made at 3 to 6 month intervals.

2.2 Prevention of Postmenopausal Osteoporosis

Start therapy with MINIVELLE 0.025 mg per day applied to the skin twice weekly. The dose may be adjusted as necessary.

2.3 Patch Application Instructions

The adhesive side of MINIVELLE should be placed on a clean, dry area on the lower abdomen (below the umbilicus) or buttocks. MINIVELLE should not be applied to the breasts**.**

MINIVELLE should be replaced twice weekly (every 3-4 days).

The sites of application must be rotated, with an interval of at least 1 week allowed between applications to a particular site.

The area selected should not be oily, damaged, or irritated. The waistline should be avoided, since tight clothing may rub the system off. The system should be applied immediately after opening the pouch and removing the protective liner. The system should be pressed firmly in place with the palm of the hand for about 10 seconds, making sure there is good contact with the skin, especially around the edges. In the event that a system should fall off, the same system may be reapplied. If the same system cannot be reapplied, a new system should be applied to another location. If a woman has forgotten to apply a patch, she should apply a new patch as soon as possible. In either case, the original treatment schedule should be continued. The interruption of treatment in women taking MINIVELLE might increase the likelihood of breakthrough bleeding, spotting and recurrence of symptoms.

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

MINIVELLE is contraindicated in women with any of the following conditions:

- Undiagnosed abnormal genital bleeding
- Known, suspected or history of breast cancer
- Known or suspected estrogen-dependent neoplasia
- Active DVT, PE, or a history of these conditions

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