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 WITH UNOPPOSED ESTROGEN IN WOMEN WITH A UTERUS
See full prescribing information for complete boxed warning.
There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens (5.2)

RECENT MAJOR CHANGES

Boxed Warning, Cardiovascular Disorders, Breast Cancer, Probable Dementia	10/2026
Dosage and Administration, Important Use Information (2.1)	10/2026
Contraindications (4)	10/2026
Warnings and Precautions, Cardiovascular Disorders (5.1)	10/2026
Warnings and Precautions, Malignant Neoplasms (5.2)	10/2026
Warnings and Precautions, Risks Associated with Concomitant of Estrogen Plus Progestogen (5.3)	10/2026
Warnings and Precautions, Probable Dementia	removed 10/2026
Warnings and Precautions, Addition of a Progestogen When a Woman Has Not Had a Hysterectomy	removed 10/2026

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)

Limitations of Use

When prescribing solely for the treatment of postmenopausal osteoporosis, first consider the use of non-estrogen medications. Consider estrogen therapy only for women at significant risk of osteoporosis.

DOSAGE AND ADMINISTRATION

Start therapy with MINIVELLE® 0.0375 mg per day applied to the skin twice weekly for the treatment of moderate to severe vasomotor symptoms due to menopause. Dosage adjustment should be guided by the clinical response (2.1)

Start therapy with MINIVELLE 0.025 mg per day applied to the skin twice weekly for the prevention of postmenopausal osteoporosis. The dose may be adjusted as necessary (2.2)

Place MINIVELLE on a clean, dry area on the lower abdomen (below the umbilicus) or buttocks. Do not apply MINIVELLE 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

- Abnormal genital bleeding of unknow etiology (4, 5.2)
- Breast cancer or a history of breast cancer (4, 5.2)
- 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 or MI), or a history of these conditions (4, 5.1)
- Known anaphylactic reaction, angioedema, or hypersensitivity to MINIVELLE (4)
- Hepatic impairment or disease (4, 5.9)
- Protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders (4)

WARNINGS AND PRECAUTIONS

- Cardiovascular Disorders: Increased risks of PE, DVT, and stroke are reported with systemic estrogen therapy. Evaluate risk factors for arterial vascular disease and/or venous thromboembolism. Immediately discontinue MINIVELLE if a PE, DVT, or stroke occurs or is suspected. (5.1)
- 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, 5.8, 5.9)
- Monitor thyroid function in women on thyroid replacement therapy (5.10, 5.17)

ADVERSE REACTIONS

The most common adverse reactions (greater than or equal to 5 percent) with MINIVELLE are: headache, breast tenderness, back pain, pain in limb, 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 and decrease or increase the estrogen plasma concentration. (7)

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

Revised: 10/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: ENDOMETRIAL CANCER WITH UNOPPOSED ESTROGEN IN WOMEN WITH A UTERUS

- **There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestogen to estrogen-only therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.**
- **Perform adequate diagnostic measures, including directed or random endometrial sampling when indicated, to rule out malignancy in menopausal women with abnormal genital bleeding of unknown etiology *[see Warnings and Precautions (5.2)]*.**

1 INDICATIONS AND USAGE

MINIVELLE is indicated for:

1.1 Treatment of Moderate to Severe Vasomotor Symptoms Due to Menopause

1.2 Prevention of Postmenopausal Osteoporosis

Limitation of Use

When prescribing solely for the prevention of postmenopausal osteoporosis, first consider the use of non-estrogen medications. Consider estrogen therapy only for women at significant risk of osteoporosis.

2 DOSAGE AND ADMINISTRATION

2.1 Important Use Information

The timing of MINIVELLLE initiation can affect the overall benefit-risk profile. Consider initiating MINIVELLE in women < 60 years old or < 10 years since menopause onset *[see Warnings and Precautions (5), Use in Specific Populations (8.5) and Clinical Studies (14)].*

When estrogen is prescribed for a menopausal woman with a uterus, the addition of a progestogen has been shown to reduce the risk of endometrial cancer. There are possible risks associated with the use of progestogens plus estrogens that differ from those of estrogen-alone regimens. See prescribing information for progestogens indicated for the prevention of endometrial hyperplasia in non-hysterectomized menopausal women receiving estrogens *[see Warnings and Precautions (5.2, 5.3)].*

Generally, a woman without a uterus does not need to use a progestogen with estrogen therapy. In some cases, however, hysterectomized women with a history of endometriosis may benefit from the addition of a progestogen *[see Warnings and Precautions (5.13)]*.

2.2 Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

Start therapy with MINIVELLE 0.0375 mg per day applied to the skin twice weekly. Make dosage adjustments based on clinical response. Reevaluate postmenopausal women periodically as clinically appropriate to determine if treatment is still necessary.

2.3 Prevention of Postmenopausal Osteoporosis due to Menopause

2.4 Application Instructions

Place the adhesive side of MINIVELLE on a clean, dry area on the lower abdomen (below the umbilicus) or buttocks. Do not apply MINIVELLE to the breasts.

Replace MINIVELLE twice weekly (every 3-4 days).

Rotate the sites of application, with an interval of at least 1 week allowed between applications to a particular site.

Select an area for application that is not oily, damaged, or irritated. Avoid the waistline, since tight clothing may rub the system off. Apply the system immediately after opening the pouch and removing the protective liner. Press the system 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 falls off, reapply the same system or apply a new system to another location. In either case, continue the original treatment schedule. If a woman has forgotten to apply MINIVELLE, have her apply a new system as soon as possible. Apply the new system on the original treatment schedule. 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:

- Abnormal genital bleeding of unknown etiology *[see Warnings and Precautions (5.2)]*.
- Current or history of breast cancer *[see Warnings and Precautions (5.2)]*.
- Estrogen-dependent neoplasia *[see Warnings and Precautions (5.2)]*.
- Active DVT, PE, or a history of these conditions *[see Warnings and Precautions (5.1)]*.
- Active arterial thromboembolic disease (for example, stroke or MI), or a history of these

conditions *[see Warnings and Precautions (5.1)]*.

- Known anaphylactic reaction, angioedema, or hypersensitivity to MINIVELLE *[See Warnings and Precautions (5.14)]*.
- Hepatic impairment or disease *[see Warnings and Precautions (5.9)]*.
- Protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders.

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Disorder

MINIVELLE is contraindicated in women with active DVT, PE, stroke, or a history of these conditions [see Contraindications (4)]. Immediately discontinue MINIVELLE if a PE, DVT, or stroke, occurs or is suspected. If feasible, discontinue MINIVELLE at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

The safety and efficacy of MINIVELLE for the prevention of cardiovascular disorders have not been established.

The Women's Health Initiative (WHI) estrogen-alone trial reported increased risks of pulmonary embolism (PE), deep vein thrombosis (DVT), and stroke, in postmenopausal women (50 to 79 years of age, average age 63.6 years) during 7.2 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg] relative to placebo. Analyses were also conducted in women aged 50-59 years, a group of women more likely to present with new onset of moderate to severe VMS compared to women of other age groups in the trial.

Only daily oral 0.625 mg CE was studied in the WHI estrogen-alone trial. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events to lower CE doses, other routes of administration, or other estrogen products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products *[see Clinical Studies (14.3)]*.

Venous Thromboembolism

In women aged 50-59 years, the WHI estrogen-alone trial reported a relative risk for PE of 1.53 (95% confidence interval [CI], 0.63, 3.75) for CE compared to placebo, with an absolute risk difference of 4 per 10,000 women-years (WYs; 10 versus 6). The relative risk for DVT was 1.66 (95% CI, 0.75, 3.67) for CE compared to placebo, with a risk difference of 5 per 10,000 WYs (13 versus 8).

In the overall study population of women aged 50-79 years, the WHI estrogen-alone trial reported a relative risk of PE of 1.35 (95% CI, 0.89, 2.05) for CE compared to placebo, with a risk difference of 4 per 10,000 WYs (14 versus 10). The relative risk for DVT was 1.48 (95% CI,

1.06, 2.07) for CE compared to placebo, with a risk difference of 7 per 10,000 WYs (23 versus 15) *[see Clinical Studies (14.3)]*.

Stroke

In women aged 50-59 years, the WHI estrogen-alone trial reported a relative risk for stroke of 0.99 (95% CI 0.53, 1.85) for CE compared to placebo, with a risk difference of -1 per 10,000 WYs (16 versus 17).

In the overall study population of women aged 50-79 years, the WHI estrogen-alone trial reported a relative risk for stroke of 1.35 (95% CI, 1.07, 1.70) for CE compared to placebo, with a risk difference of 11 per 10,000 WYs (45 versus 34) *[see Clinical Studies (14.3)]*.

5.2 Malignant Neoplasms

Endometrial Cancer

In MINIVELLE-treated menopausal women with a uterus with persistent or recurring abnormal genital bleeding of unknown etiology, perform adequate diagnostic measures, including directed or random endometrial sampling when indicated, to assess for endometrial cancer.

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in women with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in non-users and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with the use of estrogens for less than 1 year. The greatest risk appears to be associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more. This risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose.

Adding a progestogen to estrogen-alone therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. There are, however, possible risks associated with the use of progestogens plus estrogens that differ from those of estrogen-alone regimens *[see Warnings and Precautions (5.3)]*.

Breast Cancer

Assess risk and provide surveillance measures for breast cancer, such as breast examinations and mammography. The use of estrogen-alone therapy has been reported to result in an increase in abnormal mammograms requiring further evaluation.

In the WHI estrogen-alone trial, after a median follow-up of 7.2 years , daily CE-alone was not associated with an increased risk of invasive breast cancer. Among women 50-59 years old, the relative risk was 0.82 (95% CI, 0.50, 1.34) for CE compared to placebo, with a risk difference of -5 per 10,000 WYs (24 versus 29). In the overall study population of women aged 50-79 years

(average age 63.6 years), the relative risk was 0.79 (95% CI, 0.61, 1.02), with a risk difference of -7 per 10,000 WYs (28 versus 35). *[see Clinical Studies (14.3)]*. However, a large meta-analysis including 24 prospective studies of postmenopausal women comparing current use of estrogen-only products with use duration of 5 to 14 years (average of 9 years) versus never use reported a relative risk for breast cancer of 1.33 (95% CI, 1.28 to 1.38).[2]

Ovarian Cancer

A large meta-analysis including 17 prospective studies of postmenopausal women compared current use of estrogen-only products versus never use and reported a relative risk for ovarian cancer of 1.37 (95% CI, 1.26 to 1.50). The duration of hormone therapy use that was associated with an increased risk of ovarian cancer is unknown.[3]

5.3 Risks Associated with Co-administration of Estrogen Plus Progestogen

If MINIVELLE is administered with a progestogen, there are possible risks associated with the use of progestogens plus estrogens that differ from those of estrogen-alone regimens. Refer to prescribing information for progestogens indicated for the prevention of endometrial hyperplasia in non-hysterectomized menopausal women receiving estrogens.

5.4 Gallbladder Disease

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

5.5 Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in women with breast cancer and bone metastases. Discontinue estrogens, including MINIVELLE, if hypercalcemia occurs, and take appropriate measures to reduce the serum calcium level.

5.6 Visual Abnormalities

Retinal vascular thrombosis has been reported in women receiving estrogens. Discontinue MINIVELLE pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. Permanently discontinue estrogens, including MINIVELLE, if examination reveals papilledema or retinal vascular lesions.

5.7 Elevated Blood Pressure

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogens on blood pressure was not seen.

5.8 Exacerbation of Hypertriglyceridemia

In women with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Discontinue MINIVELLE if pancreatitis occurs.

5.9 Hepatic Impairment and/or Past History of Cholestatic Jaundice

Estrogens may be poorly metabolized in women with hepatic impairment. Exercise caution in any woman with a history of cholestatic jaundice associated with past estrogen use or with pregnancy. In the case of recurrence of cholestatic jaundice, discontinue MINIVELLE.

5.10 Exacerbation of Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. Monitor thyroid function in these women during treatment with MINIVELLE to maintain their free thyroid hormone levels in an acceptable range.

5.11 Fluid Retention

Estrogens may cause some degree of fluid retention. Monitor any woman with a condition(s) that might predispose her to fluid retention, such as cardiac or renal impairment. Discontinue estrogen-alone therapy, including MINIVELLE, with evidence of medically concerning fluid retention.

5.12 Hypocalcemia

Estrogen-induced hypocalcemia may occur in women with hypoparathyroidism. Consider whether the benefits of estrogen therapy, including MINIVELLE, outweigh the risks in such women.

5.13 Malignant Transformation of Endometriosis

A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen-alone therapy. Consider the addition of progestogen therapy for women known to have residual endometriosis post-hysterectomy.

5.14 Severe Anaphylactic/Anaphylactoid Reactions and Hereditary Angioedema

A few cases of anaphylactic/anaphylactoid reactions are reported in the postmarketing use of MINIVELLE. Involvement of skin (hives, pruritus, swollen lips-tongue-face) and either

respiratory tract (respiratory compromise) or gastrointestinal tract (abdominal pain, vomiting) are noted.

Angioedema involving eye/eyelid, face, larynx, pharynx, tongue and extremity (hands, legs, ankles, and fingers) with or without urticaria requiring medical intervention are reported in the postmarketing use of MINIVELLE. Angioedema involving the tongue, glottis, or larynx, may result in airway obstruction. Do not give MINIVELLE to any woman who develops angioedema during treatment with MINIVELLE.

Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema. Consider whether the benefits of estrogen therapy outweigh the risks in such women.

5.15 Exacerbation of Other Conditions

Estrogen therapy, including MINIVELLE, may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraines, porphyria, systemic lupus erythematosus, and hepatic hemangiomas. Consider whether the benefits of estrogen therapy outweigh the risks in such women.

5.16 Laboratory Tests

Serum follicle stimulating hormone (FSH) and estradiol levels have not been shown to be useful in the management of postmenopausal women with moderate to severe vasomotor symptoms.

5.17 Drug-Laboratory Test Interactions

- Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex; and beta-thromboglobulin; decreased levels of antifactor Xa and antithrombin III; decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.
- Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone levels, as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered. Women on thyroid replacement therapy may require higher doses of thyroid hormone.
- Other binding proteins may be elevated in serum, for example, corticosteroid-binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations, such as testosterone and estradiol, may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

- Increased plasma high-density lipoprotein (HDL) and HDL2 cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentration, and increased triglycerides levels.
- Impaired glucose tolerance.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in labeling:

- Cardiovascular Disorders *[see Warning and Precaution, (5.1)]*
- Malignant Neoplasms *[see **Boxed Warning**, Warnings and Precautions (5.2)]*

6.1 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.

There were no clinical trials conducted with MINIVELLE. MINIVELLE is bioequivalent to Vivelle®. The following adverse reactions are reported with Vivelle therapy:

Table 1: Summary of Most Frequently Reported Adverse Reactions (Vivelle versus Placebo) Regardless of Relationship Reported at a Frequency ≥5 Percent

	Vivelle 0.025 mg/day† (N=47) N (%)	**Vivelle 0.0375 mg/day† (N=130) N (%)**	**Vivelle 0.05 mg/day† (N=103) N (%)**	**Vivelle 0.075 mg/day† (N=46) N (%)**	**Vivelle 0.1 mg/day† (N=132) 2 N (%)**	**Placebo (N=157) N (%)**
Gastrointestinal disorders						
Constipation	2 (4.3)	5 (3.8)	4 (3.9)	3 (6.5)	2 (1.5)	4 (2.5)
Dyspepsia	4 (8.5)	12 (9.2)	3 (2.9)	2 (4.3)	0	10 (6.4)
Nausea	2 (4.3)	8 (6.2)	4 (3.9)	0	7 (5.3)	5 (3.2)
General disorders and administration site conditions* **						
Influenza-like illness	3 (6.4)	6 (4.6)	8 (7.8)	0	3 (2.3)	10 (6.4)
Pain NOS*	0	8 (6.2)	0	2 (4.3)	7 (5.3)	7 (4.5)
Infections and infestations						

Influenza	4 (8.5)	4 (3.1)	6 (5.8)	0	10 (7.6)	14 (8.9)
Nasopharyngitis	3 (6.4)	16 (12.3)	10 (9.7)	9 (19.6)	11 (8.3)	24 (15.3)
Sinusitis NOS*	4 (8.5)	17 (13.1)	13 (12.6)	3 (6.5)	7 (5.3)	16 (10.2)
Upper respiratory tract infection NOS*	3 (6.4)	8 (6.2)	11 (10.7)	4 (8.7)	6 (4.5)	9 (5.7)
Investigations						
Weight increased	4 (8.5)	5 (3.8)	2 (1.9)	2 (4.3)	0	3 (1.9)
Musculoskeletal and connective tissue disorders						
Arthralgia	0	11 (8.5)	4 (3.9)	2 (4.3)	5 (3.8)	9 (5.7)
Back pain	4 (8.5)	10 (7.7)	9 (8.7)	4 (8.7)	14 (10.6)	10 (6.4)
Neck pain	3 (6.4)	4 (3.1)	4 (3.9)	0	6 (4.5)	2 (1.3)
Pain in limb	0	10 (7.7)	7 (6.8)	2 (4.3)	6 (4.5)	9 (5.7)
Nervous system disorders						
Headache NOS*	7 (14.9)	35 (26.9)	32 (31.1)	23 (50.0)	34 (25.8)	37 (23.6)
Sinus headache	0	12 (9.2)	5 (4.9)	5 (10.9)	2 (1.5)	8 (5.1)
Psychiatric disorders						
Anxiety NEC**	3 (6.4)	5 (3.8)	0	0	2 (1.5)	4 (2.5)
Depression	5 (10.6)	4 (3.1)	7 (6.8)	0	4 (3.0)	6 (3.8)
Insomnia	3 (6.4)	6 (4.6)	4 (3.9)	2 (4.3)	2 (1.5)	9 (5.7)
Reproductive system and breast disorders						
Breast tenderness	8 (17.0)	10 (7.7)	8 (7.8)	3 (6.5)	17 (12.9)	0
Dysmenorrhea	0	0	0	3 (6.5)	0	0
Intermenstrual bleeding	3 (6.4)	9 (6.9)	6 (5.8)	0	14 (10.6)	7 (4.5)
Respiratory, thoracic and mediastinal disorders						

Sinus congestion	0	4 (3.1)	3 (2.9)	3 (6.5)	6 (4.5)	7 (4.5)
Vascular disorders						
Hot flushes NOS*	3 (6.4)	0	3 (2.9)	0	0	6 (3.8)
Hypertension NOS*	2 (4.3)	0	3 (2.9)	0	0	2 (1.3)

† Represents milligrams of estradiol delivered daily by each system

*NOS represents not otherwise specified

**NEC represents not elsewhere classified

***Application site erythema and application site irritation were observed in 3.2% or less of patients across

treatment groups.

During the clinical pharmacology studies with MINIVELLE, 35 percent or less of subjects experienced barely perceptible erythema. No transdermal systems were removed due to irritation. Three subjects (2.2 percent) reported mild discomfort while wearing MINIVELLE (N=136).

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of MINIVELLE. 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.

Breast

Breast enlargement

Cardiovascular

Palpitations, angina unstable

Gastrointestinal

Hemorrhage, diarrhea

Skin

Application site reactions, erythema, rash, hyperhidrosis, pruritis, urticaria

Central Nervous System

Dizziness, paresthesia, migraine, mood swings, emotional disorder, irritability, nervousness

Miscellaneous

Portal vein thrombosis, dyspnea, malaise, fatigue, peripheral edema, muscle spasms, paresthesia oral, swollen tongue, lip swelling, pharyngeal edema

7 DRUG INTERACTIONS

In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's wort (*Hypericum perforatum*) preparations, phenobarbital, carbamazepine and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, and grapefruit juice may increase plasma concentrations of estrogens and may result in adverse reactions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

MINIVELLE is not indicated for use in pregnancy. There are no data with the use of MINIVELLE in pregnant women; however, epidemiologic studies and meta-analyses have not found an increased risk of genital or nongenital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to combined hormonal contraceptives (estrogens and progestins) before conception or during early pregnancy.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary

Estrogens are present in human milk and can reduce milk production in breast-feeding women. This reduction can occur at any time but is less likely to occur once breast-feeding is well established.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for MINIVELLE and any potential adverse effects on the breastfed child from MINIVELLE or from the underlying maternal condition.

8.4 Pediatric Use

MINIVELLE is not indicated for use in pediatric patients. Clinical studies have not been conducted in the pediatric population.

8.5 Geriatric Use

There have not been sufficient numbers of geriatric women involved in clinical studies utilizing MINIVELLE to determine whether those over 65 years of age differ from younger subjects in their response to MINIVELLE.

The Women's Health Initiative Studies

In the WHI estrogen-alone trial (daily CE [0.625 mg]-alone versus placebo), there was a higher relative risk of stroke in women greater than 65 years of age *[see Clinical Studies (14.3)]*.

The Women's Health Initiative Memory Study

In the WHIMS ancillary study of postmenopausal women 65 to 79 years of age, there was an increased risk of probable dementia in women receiving estrogen-alone *[see Clinical Studies (**14.3**)]*.

Since the trial was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger menopausal women *[see Clinical Studies (**14.3**)]*. The safety and efficacy of MINIVELLE for the prevention of dementia has not been established.

10 OVERDOSAGE

Overdosage of estrogen may cause nausea, vomiting, breast tenderness, abdominal pain, drowsiness and fatigue, and withdrawal bleeding may occur in women. Treatment of overdose consists of discontinuation of MINIVELLE therapy with institution of appropriate symptomatic care.

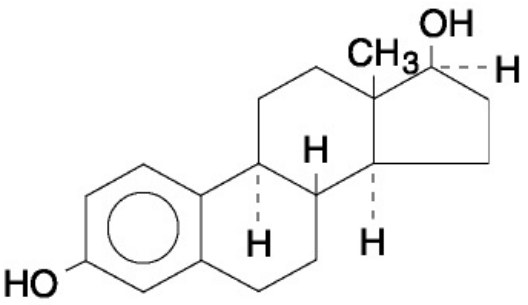
11 DESCRIPTION

MINIVELLE (estradiol transdermal system) contains estradiol in a multipolymeric adhesive. The system is designed to release estradiol continuously upon application to intact skin.

Five dosage strengths of MINIVELLE are available to provide nominal *in vivo* delivery rates of 0.025, 0.0375, 0.05, 0.075, or 0.1 mg of estradiol per day via the skin. Each corresponding system has an active surface area of 1.65, 2.48, 3.30, 4.95, or 6.6 cm^2 and contains 0.41, 0.62, 0.83, 1.24, or 1.65 mg of estradiol USP, respectively. The composition of the systems per unit area is identical.

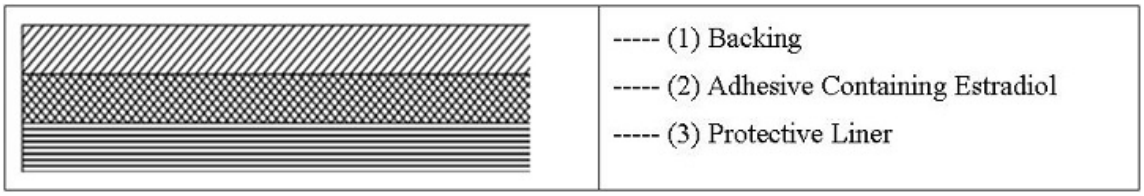
Estradiol USP is a white, crystalline powder, chemically described as estra-1,3,5 (10)-triene-3,17β-diol.

The structural formula is



The molecular formula of estradiol is $C_{18}H_{24}O_2$. The molecular weight is 272.39

MINIVELLE is comprised of three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a polyolefin laminate backing (2) an adhesive formulation containing estradiol, acrylic adhesive, silicone adhesive, oleyl alcohol, NF, povidone, USP and dipropylene glycol, and (3) a polyester release liner which is attached to the adhesive surface and must be removed before the system can be used.



The active component of the system is estradiol. The remaining components of the system are pharmacologically inactive.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone in the peripheral tissues. Thus, estrone and the sulfate

conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

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.

12.2 Pharmacodynamics

Generally, a serum estrogen concentration does not predict an individual woman's therapeutic response to MINIVELLE nor her risk for adverse outcomes. Likewise, exposure comparisons across different estrogen products to infer efficacy or safety for the individual woman may not be valid.

12.3 Pharmacokinetics

Absorption

In a single-dose, two way-crossover clinical study conducted in 96 healthy, non-smoking postmenopausal women under fed condition, MINIVELLE (0.1 mg per day) was bioequivalent to Vivelle (0.1 mg per day) based on estradiol exposure (AUC_{0-84}) and estradiol peak concentration (C_{max}) following a single-dose on the lower abdomen for 84 hours.

Estradiol pharmacokinetics were characterized in a separate open-label, single-center, randomized, single-dose, three-way crossover study conducted in 36 healthy, non-smoking postmenopausal women (aged 40 to 65 years). MINIVELLE transdermal systems delivering nominal estradiol of approximately 0.025 mg, 0.05 mg, and 0.1 mg per day were applied to the lower abdomen under fed state in a crossover fashion for 84 hours. The mean estradiol pharmacokinetics parameters are summarized in Table 2. AUC and C_{max} are dose proportional from 0.025 mg to 0.1 mg per day.

Table 2: Mean (SD) Serum Pharmacokinetic Parameters of Baseline-Uncorrected Estradiol following a Single Dose of MINIVELLE (N=36)

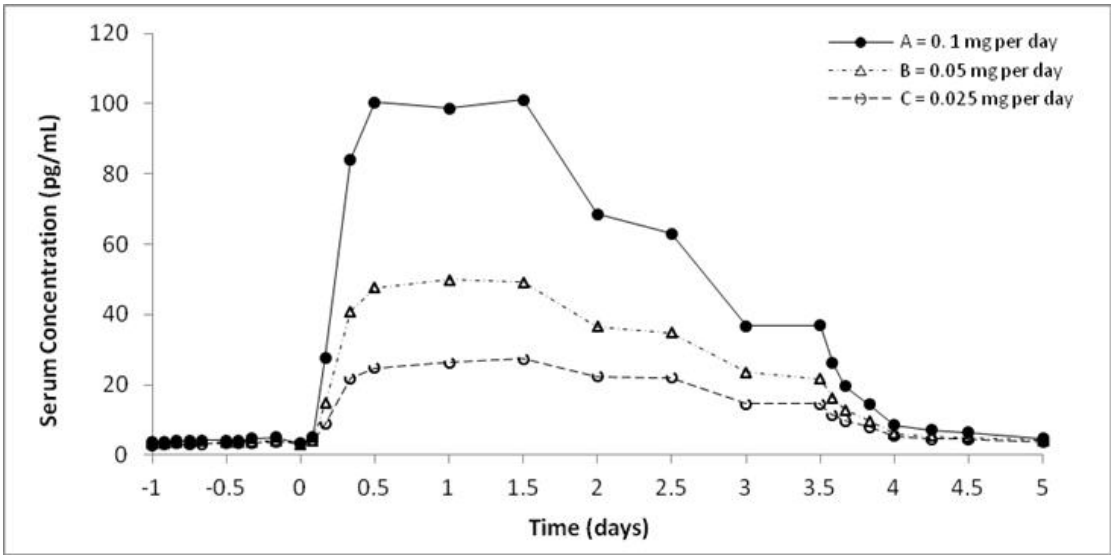
Parameter	0.1 mg/day	0.05 mg/day	0.025 mg/day
AUC_{84} (pg·hr/mL)	5875 (1857)	3057 (980)	1763 (600)
AUC_{120} (pg·hr/mL)	6252 (1938)	3320 (1038)	1979 (648)
C_{max} (pg/mL)	117 (39.3)	56.6 (17.6)	30.3 (11.1)

T_{max} (hr) [a]	24.0 (8-60)	24.0 (8-60)	36.0 (8-84)

[a]Median (minimum-maximum)

Figure 1 illustrates the mean baseline-uncorrected estradiol serum concentrations of MINIVELLE at three different strengths.

Figure 1: Mean Baseline-Uncorrected Estradiol Serum Concentration-Time Profiles Following a Single Dose of MINIVELLE 0.1 mg per day (Treatment A), 0.05 mg per day (Treatment B), and 0.025 mg per day (Treatment C) (N=36)



Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone-binding globulin (SHBG) and albumin.

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is a major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the intestine followed by reabsorption. In postmenopausal

women a significant portion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Excretion

Estradiol, estrone and estriol are excreted in the urine along with glucuronide and sulfate conjugates. The mean half-life values of estradiol calculated from treatment groups in the bioequivalence study and dose-proportionality study after dosing with MINIVELLE ranged from 6.2 to 7.9 hours. After removal of the transdermal systems, serum concentrations of estradiol and estrone returned to baseline concentrations within 24 hours.

Adhesion and Adhesive Residue

Based on combined data from bioequivalence and dose proportionality studies consisting of 208 MINIVELLE observations, approximately 98 percent of the observations had an adhesion score of 0 (i.e., the skin adhesion rate was greater than or equal to 90 percent) over the 84-hour wear period. One woman had a complete detachment during the wear period. Approximately 65 percent of the transdermal systems evaluated in these studies were with MINIVELLE 0.1 mg per day (6.6 cm^2 active surface area).

After removal of MINIVELLE, women had either no adhesive residue (score of 0) or light adhesive residue (score of 1). No woman had medium adhesive residue. Of the 208 MINIVELLE observations, 54 percent had light adhesive residue and 46 percent had no adhesive residue.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term, continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

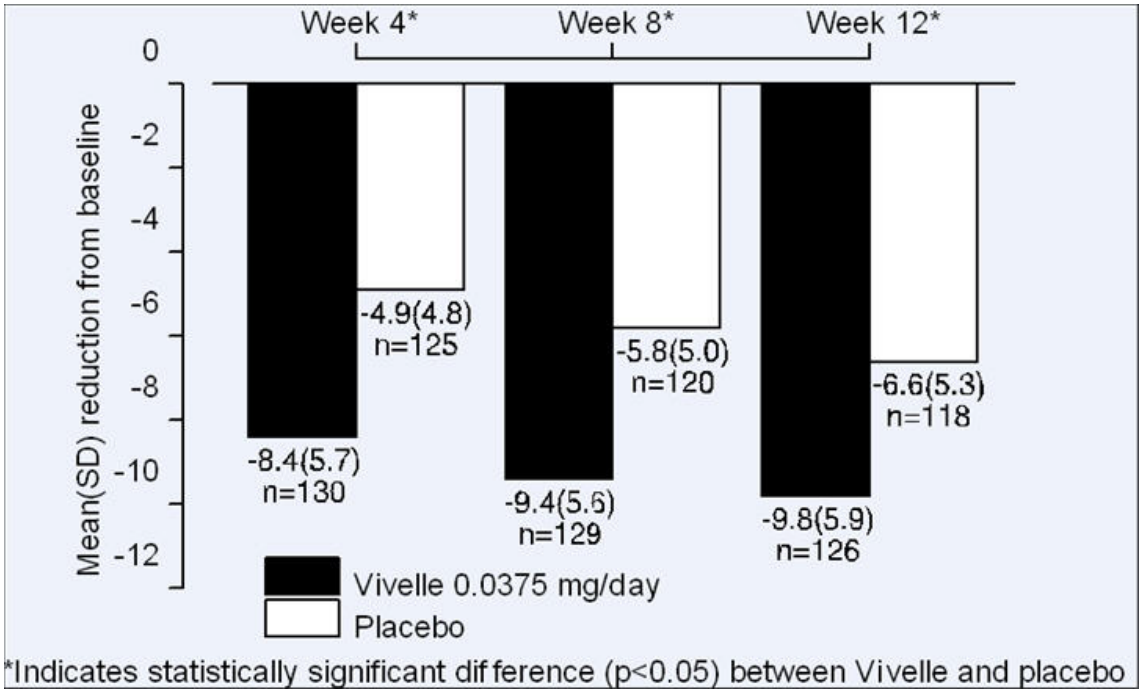
14 CLINICAL STUDIES

14.1 Effects on Vasomotor Symptoms in Postmenopausal Women

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

In two controlled clinical trials with Vivelle, in a total of 356 women, 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 women 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 women 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.

14.2 Effects on Bone Mineral Density in Postmenopausal Women

There have been no bone efficacy and safety trials conducted with MINIVELLE. In a pharmacokinetic study, MINIVELLE 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/cm2) were enrolled in this study; 194 women were randomized to one of the four doses of Vivelle (0.1, 0.05, 0.0375, or 0.025 mg/day) and 67 women 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.

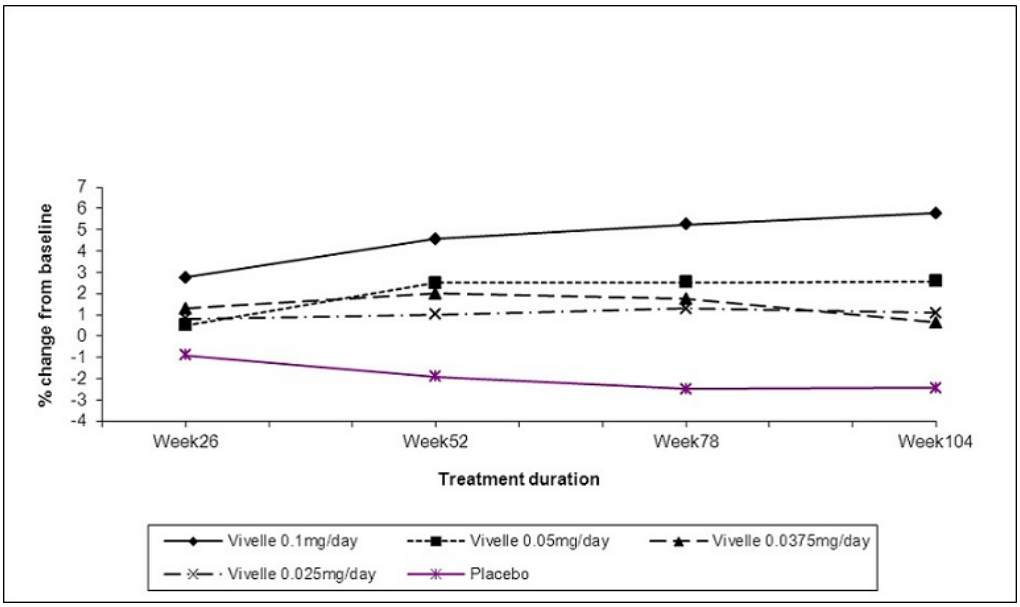
The study population comprised naturally (82 percent) or surgically (18 percent) menopausal, hysterectomized (61 percent) or non-hysterectomized (39 percent) women with a mean age of 52.0 years (range 27 to 62 years); the mean duration of menopause was 31.7 months (range 2 to

72 months). Two hundred thirty-two (89 percent) randomized women (173 on active drug, 59 on placebo) contributed data to the analysis of percent change from baseline in bone mineral density (BMD) of the AP lumbar spine, the primary efficacy variable. Women were given supplemental dietary calcium (100 mg elemental calcium/day) but no supplemental vitamin D. 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 (See Figure 3).

Figure 3: Bone mineral density – AP Lumbar spine

Least squares means of percentage change from baseline

All randomized women with at least one post-baseline assessment available with last post-baseline observation carried forward

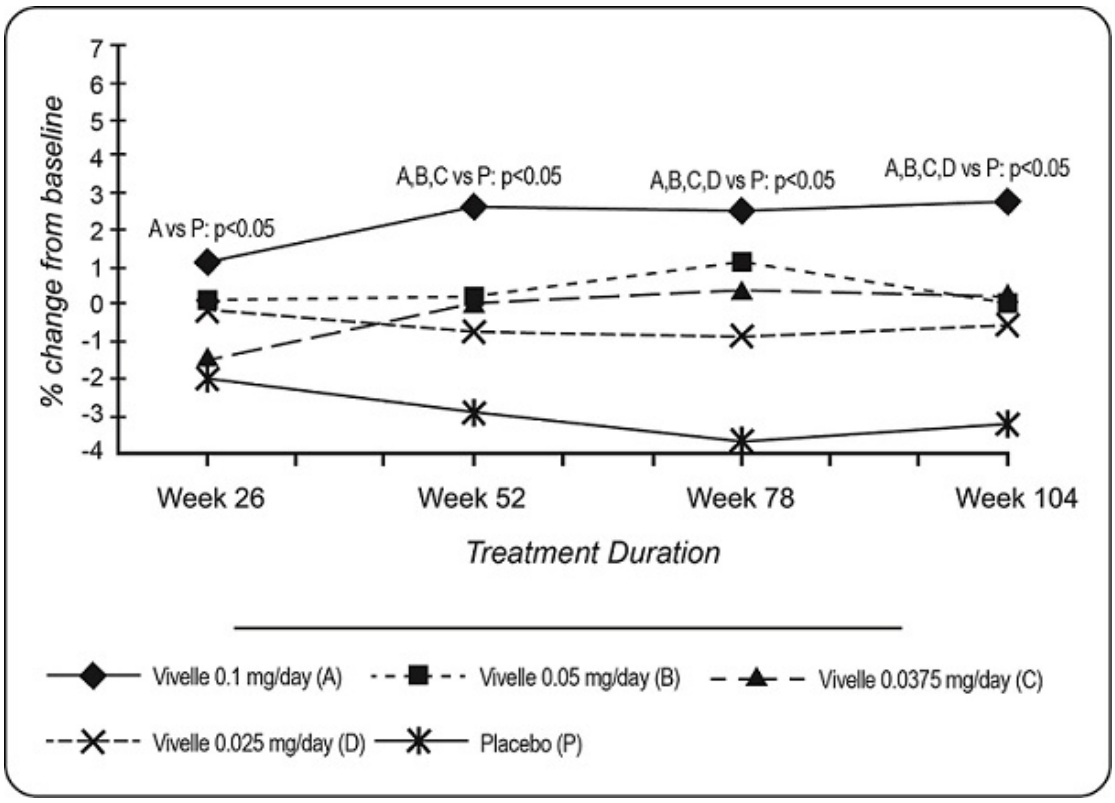


Analysis of percent change from baseline in femoral neck BMD, a secondary efficacy outcome variable, showed qualitatively similar results; all doses of Vivelle were significantly superior to placebo ($p<0.05$) at 24 months. The highest Vivelle dose was superior to placebo at all time points. A mixture of significant and non-significant results were obtained for the lower dose groups at earlier time points. The highest Vivelle dose was superior to the three lower doses, and there were no significant differences among the three lower doses at this skeletal site (see Figure 4).

Figure 4: Bone mineral density - Femoral neck

Least squares means of percentage change from baseline

All randomized women with at least one post-baseline assessment available with last post-baseline observation carried forward



14.3 Women's Health Initiative Estrogen-Alone Trial

The WHI estrogen-alone trial enrolled predominantly healthy postmenopausal women to assess the risks and benefits of daily oral CE (0.625 mg)-alone compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of CHD (defined as nonfatal MI, silent MI and CHD death), with invasive breast cancer as the primary adverse outcome. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, PE, colorectal cancer, hip fracture, or death due to other cause. This trial did not evaluate the effects of CE-alone on menopausal symptoms.

The WHI estrogen-alone trial was stopped early because an increased risk of stroke was observed, and it was deemed that no further information would be obtained regarding the risks and benefits of estrogen-alone in predetermined primary endpoints. Centrally adjudicated results for stroke events, after a median follow-up of 7.2 years, reported estrogen-alone increased the

risk for stroke in overall population compared to placebo, but this excess risk was not present in the 50-59 years subgroup examined.

No overall difference for primary CHD events (nonfatal MI, silent MI and CHD death) and invasive breast cancer incidence in women receiving CE-alone compared to placebo was reported in final centrally adjudicated results from the estrogen-alone trial, after a median follow-up of 7.2 years.[4,5]

Results of the estrogen-alone trial, which included 10,739 women (average age of 63.6 years, range 50 to 79 years; 75.3% White, 15.1% Black, 6.1% Hispanic, 3.6% Other), after a median follow-up of 7.2 years are presented in Table 3.

Table 3: Relative Risk and Risk Difference Observed in the WHI Estrogen-Alone Trial at a Median of 7.2 Years of Follow-up[a,b]

Event	Relative Ratio (95% CI)[c]	Risk Difference (CE vs placebo/10,000 WYs)[d]
CHD events	0.94 (0.78-1.14)	-3 (55 vs 58)
Non-fatal MI	*0.97 (0.79-1.21)*	*-1 (44 vs 45)*
CHD death	*1.00 (0.77-1.31)*	*0 (29 vs 29)*
All Strokes	1.35 (1.07-1.70)	11 (45 vs 34)
Deep vein thrombosis[e]	1.48 (1.06-2.07)	7 (23 vs 15)
Pulmonary embolism	1.35 (0.89-2.05)	4 (14 vs 10)
Invasive breast cancer[f]	0.79 (0.61-1.02)	-7 (28 vs 35)
Colorectal cancer	1.15 (0.81-1.64)	2 (17 vs 15)
Hip fracture	0.67 (0.46-0.96)	-6 (13 vs 19)
Vertebral fractures[e]	0.64 (0.44-0.93)	-6 (12 vs 18)
Total fractures[e]	0.72 (0.64-0.80)	-61 (153 vs 214)
Overall mortality	1.03 (0.88-1.21)	3 (80 vs 77)
Global Index[g]	1.03 (0.93-1.13)	4 (208 vs 204)

[a] Adapted from 2013 WHI trial (CE n=5,310, placebo n=5,429). WHI publications can be viewed at www.nhlbi.nih.gov/whi.

[b] Results are based on centrally adjudicated data.

[c] In the WHI studies, hazard ratios were estimated using Cox proportional hazards models comparing treatment to placebo; however, they are described here as relative risks. Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

[d] The integer representation of the risk difference may not be the numerical difference of the drug vs placebo risk due to calculations performed prior to rounding.

[e] Not included in "global index."

[f] Includes metastatic and non-metastatic breast cancer with the exception of in situ cancer.

[g] A subset of the events was combined in a "global index," defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, PE, colorectal cancer, hip fracture, or death due to other causes.

Timing of the initiation of estrogen-alone therapy relative to the start of menopause may affect the overall risk benefit profile. The study results for women 50-59 years old in the WHI estrogen-alone trial are shown in Table 4.

Table 4: Relative Risk and Risk Difference Observed Among Women 50-59 Years of Age in the WHI Estrogen – Alone Trial at a Median of 7.2 Years[a,b]

Event	**Relative Ratio (95% CI)[c]**	**Risk Difference (CE vs placebo/10,000 WYs)[d]**
CHD events	0.60 (0.35-1.04)	-11 (17 vs 28)
Non-fatal MI	*0.55 (0.31-1.00)*	*-11 (14 vs 25)*
CHD death	*0.80 (0.32-2.04)*	*-1 (7 vs 8)*
All Strokes	0.99 (0.53-1.85)	-1 (16 vs 17)
Deep vein thrombosis[e]	1.66 (0.75-3.67)	5 (13 vs 8)
Pulmonary embolism	1.53 (0.63-3.75)	3 (10 vs 6)
Invasive breast cancer[f]	0.82 (0.50-1.34)	-5 (24 vs 29)
Colorectal cancer	0.71 (0.30-1.67)	-3 (7 vs 10)
Hip fracture	5.01 (0.59-42.91)	3 (3 vs 1)
Vertebral fractures[e]	0.50 (0.17-1.47)	-4 (4 vs 8)
Total fractures[e]	0.90 (0.72-1.11)	-16 (133 vs 149)
Overall mortality	0.70 (0.46-1.09)	-11 (29 vs 40)

Global Index[g]	0.84 (0.66-1.07)	-19 (98 vs 117)

[a] Adapted from 2013 WHI trial (CE n=1,639; placebo n=1,674). WHI publications can be viewed at www.nhlbi.nih.gov/whi.

[b] Results are based on centrally adjudicated data.

[c] In the WHI studies, hazard ratios were estimated using Cox proportional hazards models comparing treatment to placebo; however, they are described here as relative risks. Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.

[d] The integer representation of the risk difference may not be the numerical difference of the drug vs placebo risk due to calculations performed prior to rounding.

[e] Not included in "global index."

[f] Includes metastatic and non-metastatic breast cancer with the exception of in situ cancer.

[g] A subset of the events was combined in a "global index," defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, PE, colorectal cancer, hip fracture, or death due to other causes.

14.4 Women's Health Initiative Memory Study (WHIMS)

The WHIMS estrogen-alone ancillary study of WHI enrolled 2,947 predominantly healthy hysterectomized postmenopausal women 65 to 79 years of age (45% were 65 to 69 years of age, 36% were 70 to 74 years of age, and 19% were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg)-alone on the incidence of probable dementia (primary outcome) compared to placebo. Probable dementia as defined in this study included Alzheimer's disease (AD), vascular dementia (VaD) and mixed type (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD.[6]

Based on updated data after a median follow-up of 7.2 years, the relative risk of probable dementia for CE- alone versus placebo was 1.47 (95% CI, 0.85-2.52). The absolute risk of probable dementia for CE-alone versus placebo was 33 versus 22 cases per 10,000 women-years.[1] Since analysis was performed on women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women *[see Use in Specific Populations (8.5)]*.

15 REFERENCES

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3. Collaborative Group On Epidemiological Studies Of Ovarian Cancer; Beral V, Gaitskell K, Hermon C, Moser K, Reeves G, Peto R. Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies. Lancet. 2015 May 9;385(9980):1835-42.
4. Anderson GL, et al; Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA. 2004 Apr 14;291(14):1701-12.
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6. Espeland MA, Rapp SR, Shumaker SA, Brunner R, Manson JE, Sherwin BB, Hsia J, Margolis KL, Hogan PE, Wallace R, Dailey M, Freeman R, Hays J; Women's Health Initiative Memory Study. Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. JAMA. 2004 Jun 23;291(24):2959-68.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

MINIVELLE (estradiol transdermal system), 0.025 mg per day - each 1.65 cm^2 system contains 0.41 mg of estradiol USP for nominal* delivery of 0.025 mg of estradiol per day.

Patient Calendar Pack of 8 Systems……..NDC 68968-6625-8

MINIVELLE (estradiol transdermal system), 0.0375 mg per day - each 2.48 cm^2 system contains 0.62 mg of estradiol USP for nominal* delivery of 0.0375 mg of estradiol per day.

Patient Calendar Pack of 8 Systems……..NDC 68968-6637-8

MINIVELLE (estradiol transdermal system), 0.05 mg per day - each 3.3 cm^2 system contains 0.83 mg of estradiol USP for nominal* delivery of 0.05 mg of estradiol per day.

Patient Calendar Pack of 8 Systems…….NDC 68968-6650-8

MINIVELLE (estradiol transdermal system), 0.075 mg per day - each 4.95 cm^2 system contains 1.24 mg of estradiol USP for nominal* delivery of 0.075 mg of estradiol per day.

Patient Calendar Pack of 8 Systems…….NDC 68968-6675-8

MINIVELLE (estradiol transdermal system), 0.1 mg per day - each 6.6 cm2 system contains 1.65 mg of estradiol USP for nominal* delivery of 0.1 mg of estradiol per day.

Patient Calendar Pack of 8 Systems…….NDC 68968-6610-8

*See Description

16.2 Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [*see USP Controlled Room Temperature*]

Do not store unpouched. Apply immediately upon removal from the protective pouch.

Used transdermal systems still contain active hormone. To discard, fold the sticky side of the transdermal system together, place it in a sturdy child-proof container, and place this container in the trash. Used transdermal systems should not be flushed in the toilet.

17 PATIENT COUNSELING INFORMATION

Advise women to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Vaginal Bleeding

Inform postmenopausal women to report unusual vaginal bleeding to their healthcare providers as soon as possible *[see Warnings and Precautions (5.2)]*

Possible Serious Adverse Reactions with Estrogen–Alone Therapy

Inform postmenopausal women of possible serious adverse reactions of estrogen-alone therapy including Cardiovascular Disorders, Malignant Neoplasms, and Probable Dementia (for persons age 65 years and older) *[see Warning and Precautions (5.1, 5.2, 8.5)]*.

Possible Common Adverse Reactions with Estrogen–Alone Therapy

Inform postmenopausal women of less serious but common adverse reactions of estrogen-alone therapy such as headache, breast pain and tenderness, nausea and vomiting.

PATIENT INFORMATION

MINIVELLE (MIN-ee-vell)

(estradiol transdermal system)

Read this Patient Information before you start using MINIVELLE and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your menopausal symptoms or your treatment.

What is the most important information I should know about MINIVELLE (an estrogen hormone)?

- Using estrogen-alone may increase your chance of getting cancer of the uterus (womb).
- Report any unusual vaginal bleeding right away while you are using MINIVELLE. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.
- Do not use estrogen-alone to prevent heart disease, heart attacks, strokes, or dementia (decline in brain function).
- Using estrogen-alone may increase your chances of getting strokes or blood clots.
- Do not use estrogens with progestogens to prevent heart disease, heart attacks, strokes, or dementia.
- Only one estrogen-alone product and dose have been shown to increase your chances of getting strokes, blood clots, and dementia.

  Because other products and doses have not been studied in the same way, it is not known how the use of MINIVELLE will affect your chances of developing these conditions. You and your healthcare provider should talk regularly about whether you still need treatment with MINIVELLE.

What is MINIVELLE?

MINIVELLE is a prescription medicine patch (transdermal system) that contains the estrogen hormone estradiol. When applied to the skin, estradiol is absorbed through the skin into the bloodstream.

What is MINIVELLE® used for?

MINIVELLE is used after menopause to:

- **Reduce moderate to severe hot flashes**
  Estrogens are hormones made by a woman's ovaries. The ovaries normally stop making

estrogens when a woman is between 45 and 55 years old. This drop in body estrogen levels causes the “change of life” or menopause (the end of monthly menstrual periods). Sometimes, both ovaries are removed during an operation before natural menopause takes place. The sudden drop in estrogen levels causes “surgical menopause.”

When estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest or sudden intense feelings of heat and sweating (“hot flashes” or “hot flushes”). In some women, the symptoms are mild and they will not need estrogens. In other women, symptoms can be more severe.

- **Help reduce your chances of getting osteoporosis (thin weak bones)**
  Osteoporosis from menopause is a thinning of the bones that makes them weaker and easier to break. If you use MINIVELLE only to prevent osteoporosis due to menopause, talk with your healthcare provider about whether a different treatment or medicine without estrogens might be better for you.

  You and your healthcare provider should talk regularly about whether you should continue treatment with MINIVELLE.

Who should not use MINIVELLE? Do not start using MINIVELLE if you:

- **have unusual vaginal bleeding**
  Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.
- **have been diagnosed with a bleeding disorder**
- **currently have or have had certain cancers**
  Estrogens may increase the chances of getting certain types of cancers, including cancer of the breast or uterus (womb). If you have or have had cancer, talk with your healthcare provider about whether you should use MINIVELLE.
- **had a stroke or heart attack**
- **currently have or have had blood clots**
- **currently have or have had liver problems**
- **are allergic to MINIVELLE or the ingredients in it**. See the list of ingredients in MINIVELLE at the end of this leaflet.

Before you use MINIVELLE, tell your healthcare provider about all of your medical conditions, including if you:

- **have any unusual vaginal bleeding**
  Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.
- **have any other medical conditions that may become worse while you are using MINIVELLE**

Your healthcare provider may need to check you more carefully if you have certain conditions such as asthma (wheezing), diabetes, epilepsy (seizures), migraine, endometriosis, lupus, angioedema (swelling of the face and tongue), problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.

- **are going to have surgery or will be on bed rest**

  Your healthcare provider will let you know if you need to stop using MINIVELLE

- **are pregnant or think you may be pregnant.**

  MINIVELLE is not for pregnant women.

- **are breast feeding**

  The hormone in MINIVELLE can pass into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. Some medicines may affect how MINIVELLE works. MINIVELLE may also affect how your other medicines work. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I use MINIVELLE?

For detailed instructions, see the step-by-step instructions for using MINIVELLE at the end of this Patient Information

- Use MINIVELLE exactly as your healthcare provider tells you to use it
- MINIVELLE is for skin use only
- Change your MINIVELLE patch 2 times a week or every 3 to 4 days
- Apply your MINIVELLE patch to a clean, dry area on your lower abdomen or buttocks. This area must be clean, dry, and free of powder, oil or lotion for your patch to stick to your skin
- Apply your MINIVELLE patch to a different area of your abdomen or your buttocks each time. Do not use the same application site 2 times in the same week.
- Do not apply MINIVELLE to your breasts
- If you forget to apply a new MINIVELLE patch, apply a new patch as soon as possible.
- You and your healthcare provider should talk regularly (every 3 to 6 months) about your dose and whether you still need treatment with MINIVELLE.

How to Change MINIVELLE

- When changing the patch, peel off the used patch slowly from the skin.
- After removal of MINIVELLE if any adhesive residue remains on your skin, allow the area to dry for 15 minutes. Then, gently rub the area with oil or lotion to remove the adhesive from your skin

- Apply the new patch to a different area of your abdomen or buttocks. This area must be clean, dry, cool and free of powder, oil or lotion.

What are the possible side effects of MINIVELLE?

Side effects are grouped by how serious they are and how often they happen when you are treated.

Serious, but less common side effects include:

- heart attack
- stroke
- blood clots
- breast cancer
- cancer of the lining of the uterus (womb)
- cancer of the ovary
- dementia (for persons age 65 years and older)
- high or low blood calcium
- gallbladder disease
- visual abnormalities
- high blood pressure
- high levels of fat (triglyceride) in your blood
- liver problems
- changes in your thyroid hormone levels
- fluid retention
- cancer changes of endometriosis
- enlargement of benign tumors of the uterus ("fibroids")
- worsening of swelling of face and tongue (angioedema) in women with a history of angioedema

Call your healthcare provider right away if you get any of the following warning signs or any other unusual symptoms that concern you:

- new breast lumps
- unusual vaginal bleeding
- changes in vision or speech
- sudden new severe headaches
- severe pains in your chest or legs with or without shortness of breath, weakness and fatigue
- swelling of face and tongue with or without red, itchy bumps

Common side effects of MINIVELLE include:

- headache
- breast pain
- irregular vaginal bleeding or spotting
- stomach or abdominal cramps, bloating
- nausea and vomiting
- hair loss
- fluid retention
- vaginal yeast infection
- redness and/or irritation at patch placement site

These are not all the possible side effects of MINIVELLE. For more information, ask your healthcare provider or pharmacist. Tell your healthcare provider if you have any side effects that bother you or do not go away. You may report side effects to Noven at 1-800-455-8070 or to FDA at 1-800-FDA-1088.

What can I do to lower my chances of a serious side effect with MINIVELLE?

- Talk with your healthcare provider regularly about whether you should continue using MINIVELLE.
- If you have a uterus, talk to your healthcare provider about whether the addition of a progestogen is right for you. In general, the addition of a progestogen is generally recommended for a woman with a uterus to reduce the chance of getting cancer of the uterus (womb).
- See your healthcare provider right away if you get vaginal bleeding while using MINIVELLE.
- Have a pelvic exam, breast exam and mammogram (breast X-ray) every year unless your healthcare provider tells you something else. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often.
- If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances of getting heart disease. Ask your healthcare provider for ways to lower your chances of getting heart disease.

How should I store and throw away used MINIVELLE patches?

- Store MINIVELLE at room temperature 68°F to 77°F (20°C to 25°C)
- Do not store MINIVELLE patches outside of their pouches. Apply immediately upon removal from the protective pouch
- Used patches still contain estrogen. To throw away the patch, fold the sticky side of the patch together, place it in a sturdy child-proof container, and place this container in the trash. Used patches should not be flushed in the toilet

KEEP MINIVELLE and all other medicines out of the reach of children

General information about safe and effective use of MINIVELLE

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets. Do not use MINIVELLE for conditions for which it was not prescribed. Do not give MINIVELLE to other people, even if they have the same symptoms you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about MINIVELLE that is written for health professionals. You can get more information by calling Noven Pharmaceuticals, Inc. at 1-800-455-8070.

What are the ingredients in MINIVELLE?

Active ingredient: estradiol

Inactive ingredients: Polyolefin laminate backing, acrylic and silicone adhesives, oleyl alcohol, NF, povidone, USP and dipropylene glycol and a polyester release liner

INSTRUCTIONS FOR USE

MINIVELLE® (MIN-ee-vell)

(estradiol transdermal system)

Read this PATIENT INFORMATION before you start using MINIVELLE and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your menopausal symptoms or your treatment.

You will need the following supplies **(See Figure A)**.

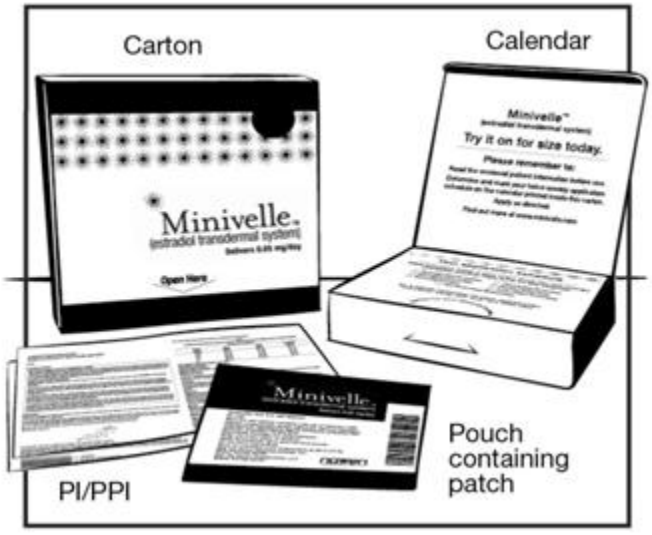


Figure A

Step 1: Pick the days you will change your patch.

- You will need to change your patch 2 times a week or every 3 to 4 days. Use the calendar printed inside your carton to choose the 2 days you will change your patch **(See Figure B)**.
- **Remember to change your patch on the same 2 days you marked on your calendar.** If you forget to change your patch on the correct date, apply a new patch as soon as you remember, and continue to follow your original schedule



Figure B

Step 2. Remove the MINIVELLE patch from the pouch.

- Remove the patch from its protective pouch by tearing at the notch (**do not** use scissors, **See Figure C**).
- Do not remove your patch from the protective pouch until you are ready to apply it



Figure C

Step 3. Remove half of the adhesive liner (See Figure D).



Figure D

Step 4. Placing the patch on your skin.

- Hold the part of the patch that still has the adhesive liner on it
- **Avoid touching the sticky half of the patch with your fingers**
- Apply the exposed sticky half of the patch to 1 of the areas of skin shown below **(See Figures E and F)**.



Figure E



Figure F

Note:

- Avoid the waistline, since clothing and belts may cause the patch to be rubbed off
- Do not apply the patch to your breasts

- Only apply the patch to skin that is clean, dry, and free of any powder, oil, or lotion
- You should not apply the patch to injured, burned, or irritated skin, or areas with skin conditions (such as birth marks, tattoos, or that is very hairy)

Step 5: Press the patch firmly onto your skin.

- Remove the remaining half of the adhesive liner and press the entire patch into place with the palm of your hand for 10 seconds
- Rub the edges of the patch with your fingers to make sure that it will stick to your skin **(See Figure G)**.

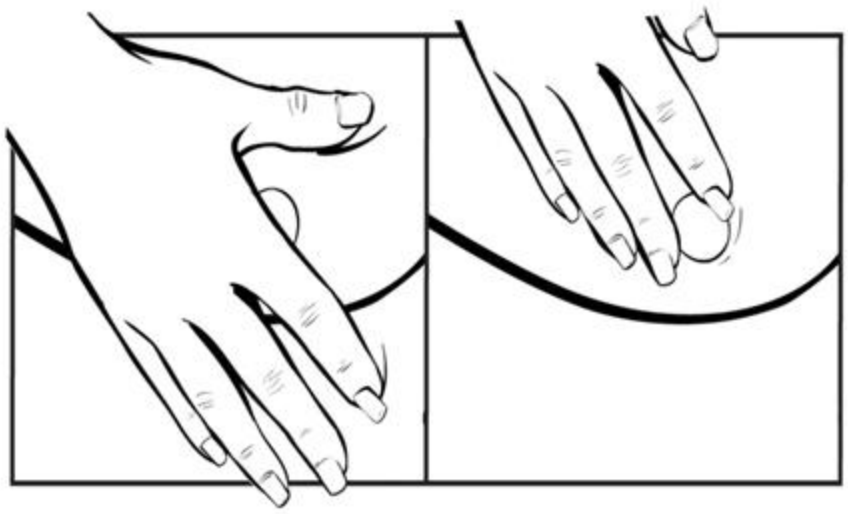


Figure G

Note:

- Showering will not cause your patch to fall off
- If your patch falls off reapply it. If you cannot reapply the patch, apply a new patch to another area **(See Figures E and D)** and continue to follow your original placement schedule
- If you stop using your MINIVELLE patch or forget to apply a new patch as scheduled, you may have spotting, or bleeding, and recurrence of symptoms

Step 6: Throwing away your used patch.

- When it is time to change your patch, remove the old patch before you apply a new patch
- To throw away the patch, fold the sticky side of the patch together, place it in a sturdy child-proof container, and place this container in the trash. Used patches should not be flushed in the toilet

This Patient Information and Instructions for Use have been approved by the U.S. Food and Drug Administration.

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Noven Pharmaceuticals Inc.
Miami, FL 33186

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