PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrActivelle®

1 mg Estradiol and
0.5 mg Norethindrone acetate, USP

Film-coated tablets

Estrogenic Hormones/Progestin

Novo Nordisk Canada Inc.
101-2476 Argentia Road
Mississauga, Ontario
L5N 6M1 Canada

Date of Initial Authorization:
2004-03-30
Date of Revision:
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RECENT MAJOR LABEL CHANGES

Not applicable.

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Activelle® (estradiol/norethindrone acetate) is indicated for:

- Treatment of moderate to severe vasomotor symptoms occurring in naturally or surgically induced estrogen deficiency states.
- Treatment of vulvar or vaginal atrophy associated with menopause.

Activelle® is recommended only in women with intact uteri since the regimen includes a progestin to prevent endometrial hyperplasia.

1.1 Pediatrics

Pediatrics (< 18 years of age): Activelle® is not indicated for use in a pediatric population. Safety and effectiveness in pediatric patients have not been established.

2 CONTRAINDICATIONS

- Patients with known hypersensitivity to this drug or any ingredient in the formulation or components of the container. For complete listing, see the 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section of the product monograph.
- Liver dysfunction or disease as long as liver function tests have failed to return to normal
- Known, suspected, or past history of estrogen-dependent or progestin-dependent malignant neoplasia (e.g. endometrial cancer)
- Endometrial hyperplasia
- Known, suspected, or past history of breast cancer
- Undiagnosed abnormal genital bleeding
- Known or suspected pregnancy
- Active or past history of arterial thromboembolic disease (e.g. stroke, myocardial infarction, coronary heart disease)
- Active or past history of confirmed venous thromboembolism (such as deep vein thrombosis or pulmonary embolism) or active thrombophlebitis
- Partial or complete loss of vision from ophthalmic vascular disease
- Porphyria
- Classical migraine
- Breastfeeding

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

The Women's Health Initiative (WHI) trial examined the health benefits and risks of oral combined *estrogen plus progestin* therapy (n=16,608) and oral *estrogen-alone* therapy (n=10,739) in postmenopausal women aged 50 to 79 years.[1-3]

The *estrogen plus* progestin arm of the WHI trial (mean age 63.3 years) indicated an increased risk of *myocardial infarction* (MI), *stroke, invasive breast cancer, pulmonary emboli* and *deep vein thrombosis* in postmenopausal women receiving treatment with combined conjugated equine estrogens (CEE, 0.625 mg/day) and medroxyprogesterone acetate (MPA, 2.5 mg/day) for 5.2 years compared to those receiving placebo.[1]

The *estrogen-alone* arm of the WHI trial (mean age 63.6 years) indicated an increased risk of *stroke* and *deep vein thrombosis* in hysterectomized women treated with CEE-alone (0.625 mg/day) for 6.8 years compared to those receiving placebo.[2]

Therefore, the following should be given serious consideration at the time of prescribing:

- Estrogens with or without progestins **should not** be prescribed for primary or secondary prevention of cardiovascular diseases.
- Estrogens with or without progestins should be prescribed at the **lowest effective dose** for the approved indication.
- Estrogens with or without progestins should be prescribed for **the shortest period** possible for the approved indication.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Activelle® is a continuous combined Hormone Replacement Therapy (HRT) intended for use in women with intact uteri. For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration should be used.

In women with amenorrhea and not taking HRT or women in transition from another continuous combined HRT product, treatment with Activelle® may be started on any convenient day. In women in transition from sequential HRT regimens, treatment should start right after their withdrawal bleeding has ended.

4.2 Recommended Dose and Dosage Adjustment

One tablet of Activelle® (estradiol 1 mg and norethindrone acetate 0.5 mg) should be taken orally once a day without interruption, preferably at the same time every day. Patients should be re-evaluated within 3-6 months after initiation of treatment, to assess response to treatment.

4.5 Missed Dose

If the patient has forgotten to take a tablet, the tablet should be taken as soon as possible within the next 12 hours. After 12 hours the tablet should be discarded and next dose taken at the normal time. Forgetting a dose may increase the likelihood of breakthrough bleeding and spotting.

5 OVERDOSAGE

Symptoms of overdose
Numerous reports of ingestion of large doses of estrogen products and estrogen-containing oral contraceptives by young children have not revealed acute serious ill effects. Overdosage with estrogen may cause nausea, vomiting, breast discomfort, fluid retention, bloating or vaginal bleeding in women. Progestin (e.g. norethindrone acetate) overdosage has been characterized by depressed mood, tiredness, acne and hirsutism.

Treatment of overdose
Symptomatic treatment should be given.

For management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Film-coated tablet 1 mg estradiol (as estradiol hemihydrate) and 0.5 mg norethindrone acetate	Copovidone, hypromellose, lactose monohydrate, magnesium stearate, maize starch, talc,triacetin.

Activelle® tablets are white, round, biconvex, film-coated tablets engraved with NOVO 288 on one side and APIS on the other side. The tablets are available in calendar dial packs of 1x28 tablets or 3x28 tablets. Each tablet contains estradiol 1 mg (as the hemihydrate) and norethindrone acetate 0.5 mg.

7 WARNINGS AND PRECAUTIONS

General
For the treatment of postmenopausal symptoms, Hormone Replacement Therapy (HRT) should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and HRT should only be continued as long as the benefit outweighs the risk.

Carcinogenesis and Mutagenesis

Breast Cancer
Available epidemiological data indicate that the use of combined *estrogen plus progestin* by postmenopausal women is associated with an increased risk of invasive breast cancer.

In the *estrogen plus progestin* arm of the WHI trial, among 10,000 women over a one-year period, there were:

- 8 more cases of invasive breast cancer (38 on combined HRT versus 30 on placebo).[1]

The WHI study also reported that the invasive breast cancers diagnosed in the *estrogen plus progestin* group were similar in histology but were larger (mean [SD], 1.7 cm [1.1] vs 1.5 cm [0.9], respectively; P=0.04) and were at a more advanced stage compared with those diagnosed in the placebo group. The percentage of women with abnormal mammograms (recommendations for short-interval follow-up, a suspicious abnormality, or highly suggestive of malignancy) was significantly higher in the *estrogen plus progestin* group versus the placebo group. This difference appeared at year one and persisted in each year thereafter.[3]

In the *estrogen-alone* arm of the WHI trial, there was no statistically significant difference in the rate of invasive breast cancer in hysterectomized women treated with conjugated equine estrogens versus women treated with placebo.[2]

It is recommended that estrogens with or without progestins not be given to women with existing breast cancer or those with a previous history of the disease (see 2 CONTRAINDICATIONS).

There is a need for caution in prescribing estrogens with or without progestins for women with known risk factors associated with the development of breast cancer, such as strong family history of breast cancer (first degree relative) or who present a breast condition with an increased risk (abnormal mammograms and/or atypical hyperplasia at breast biopsy).

Other known risk factors for the development of breast cancer such as nulliparity, obesity, early menarche, late age at first full term pregnancy and at menopause should also be evaluated.

It is recommended that women undergo mammography prior to the start of HRT treatment and at regular intervals during treatment, as deemed appropriate by the treating physician and according to the perceived risks for each patient.

Taking estrogens with progestins may increase the density of breast tissue, potentially adversely affecting the capability of mammography to detect breast cancer.

The overall benefits and possible risks of hormone replacement therapy should be fully considered and discussed with patients. It is important that the modest increased risk of being diagnosed with breast cancer after 4 years of treatment with combined estrogen plus progestin HRT (as reported in the results of the WHI trial) be discussed with the patient and weighed against its known benefits.

Instructions for regular self-examination of the breasts should be included in this counseling.

Endometrial Hyperplasia & Endometrial Carcinoma

The risk of endometrial hyperplasia and carcinoma is increased when estrogens are administered alone for prolonged periods to women with intact uteri. The role of a progestin, when combined with estrogen, is to prevent endometrial hyperplasia/carcinoma in women with intact uteri. The addition of progestin for at least 12 days per cycle in non-hysterectomised women reduces this risk.

In the WHI study, endometrial cancer rates were low and were not increased by 5 years of *estrogen plus progestin* exposure (hazard ratio 0.83 [adjusted 95% CI 0.29-2.32])[1]. Because endometrial cancer has a relatively low incidence rate, the incidence of endometrial hyperplasia is used as a surrogate endpoint in clinical studies.

In a 12 month prospective, double-blind, randomized, multicentre clinical trial of 1,176 postmenopausal women (age range 44 to 82), who were randomized to one of four arms: 1 mg estradiol unopposed (n=296), 1 mg E2 + 0.1 mg NETA (n=294), 1 mg E2 + 0.25 mg NETA (n=291), and Activelle® 1.0 mg/0.5 mg (n=295). At the end of the study, endometrial biopsy results were available for 988 subjects and the incidence of endometrial hyperplasia with Activelle® was 0.4% (one simple hyperplasia without atypia) compared with 14.6% with 1 mg unopposed estradiol.

All women taking estrogen/progestin combination should undergo clinical surveillance for endometrial abnormalities. Adequate diagnostic measures, including endometrial sampling, should be performed in all cases of undiagnosed persistent or recurring abnormal genital bleeding.

Ovarian Cancer
Some recent epidemiologic studies have found that the use of hormone replacement therapy (*estrogen-alone* and *estrogen plus progestin* therapies), in particular for 5 or more years, has been associated with an increased risk of ovarian cancer**.**

Cardiovascular
The results of the Heart and Estrogen/progestin Replacement Studies (HERS and HERS II) and the Women's Health Initiative (WHI) trial indicate that the use of *estrogen plus progestin* is associated with an increased risk of coronary heart disease (CHD) in postmenopausal women.[1,4,5] The results of the WHI trial indicate that the use of *estrogen-alone* and *estrogen plus progestin* is associated with an increased risk of stroke in postmenopausal women.[1,2]

WHI Trial Findings
In the combined *estrogen plus progestin* arm of the WHI trial, among 10,000 women over a one-year period, there were:

- 8 more cases of stroke (29 on combined HRT versus 21 on placebo)
- 7 more cases of CHD (37 on combined HRT versus 30 on placebo).

In the *estrogen-alone* arm of the WHI trial of women with prior hysterectomy, among 10,000 women over a one-year period, there were/was:

- 12 more cases of stroke (44 on *estrogen-alone* therapy versus 32 on placebo)
- No statistically significant difference in the rate of CHD.[2]

HERS and HERS II Findings
In the Heart and Estrogen/progestin Replacement Study (HERS) of postmenopausal women with documented heart disease (n=2763, average age 66.7 years), a randomized placebo-controlled clinical trial of secondary prevention of coronary heart disease (CHD), treatment with 0.625 mg/day oral conjugated equine estrogen (CEE) plus 2.5 mg oral medroxyprogesterone acetate (MPA) demonstrated no cardiovascular benefit. Specifically, during an average follow-up of 4.1 years, treatment with CEE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the hormone-treated group than in the placebo group in year 1, but not during the subsequent years.[4]

From the original HERS trial, 2321 women consented to participate in an open label extension of HERS known as HERS II. Average follow-up in HERS II was an additional 2.7 years, for a

total of 6.8 years overall. After 6.8 years, hormone therapy did not reduce the risk of cardiovascular events in women with CHD.[5]

Blood Pressure
Women using hormone replacement therapy sometimes experience increased blood pressure. Blood pressure should be monitored with HRT use. Elevation of blood pressure in previously normotensive or hypertensive patients should be investigated and HRT may have to be discontinued.

Ear/Nose/Throat

Otosclerosis
Estrogens should be used with caution in patients with otosclerosis.

Endocrine and Metabolism

Calcium and Phosphorus Metabolism
Because the prolonged use of estrogens with or without progestins influences the metabolism of calcium and phosphorus, estrogens with or without progestins should be used with caution in patients with metabolic and malignant bone diseases associated with hypercalcemia and in patients with renal insufficiency.

Glucose and Lipid Metabolism
A worsening of glucose tolerance and lipid metabolism have been observed in a significant percentage of peri- and postmenopausal patients. Therefore, diabetic patients or those with a predisposition to diabetes should be observed closely to detect any alterations in carbohydrate or lipid metabolism, especially in triglyceride blood levels.

In 38 randomized postmenopausal women (age range 53 to 70) with type 2 diabetes included in a 6-month randomised, parallel, double-blind, single-center trial randomized to one of two arms: 1 mg E2 (n=19) and 1 mg E2 + 0.5 mg NETA (n=19) showed no change over time in glycemic control as measured by fasting glucose, serum free insulin, HBA_{1c} or fructosamine. In postmenopausal women with type 2 diabetes after 6 months of treatment, diabetic women receiving Activelle® had a significant decrease over time in total cholesterol, LDL-cholesterol and lipoprotein (a), without modifying triglycerides or HDL-cholesterol levels**.**

Women with familial hyperlipidemias need special surveillance. Lipid-lowering measures are recommended additionally, before treatment is started**.** Women with pre-existing hypertriglyceridemia should be followed closely during estrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with estrogen therapy in this condition.

Hypothyroidism
Patients who require thyroid hormone replacement therapy and who are also taking estrogen should have their thyroid function monitored regularly to assure that thyroid hormone levels remain in an acceptable range (see 9.7 Drug-Laboratory Test Interactions).

Other Conditions
Activelle® contains lactose. In patient with rare hereditary galactose intolerance, lactase deficiency or glucose-galactose malabsorption, the severity of the condition should be taken into careful consideration before prescribing Activelle®. The patients should be closely monitored.

Genitourinary

Endometriosis
Symptoms and physical findings associated with a previous diagnosis of endometriosis may reappear or become aggravated with estrogen use.

Uterine Leiomyomata
Pre-existing uterine leiomyomata may increase in size during estrogen use. Growth, pain or tenderness of uterine leiomyomata requires discontinuation of medication and appropriate investigation.

Vaginal Bleeding
Breakthrough bleeding and spotting may occur during the first months of treatment. Abnormal vaginal bleeding, such as breakthrough bleeding or spotting due to its prolongation, irregularity or heaviness, occurring during therapy or continuing after treatment has been discontinued should prompt appropriate diagnostic measures, which may include endometrial biopsy to rule out the possibility of uterine malignancy and the treatment should be re-evaluated.

Hematologic

Venous Thromboembolism
Available epidemiological data indicate that use of estrogen with or without progestin by postmenopausal women is associated with an increased risk of developing venous thromboembolism (VTE).

In the *estrogen plus progestin* arm of the WHI trial, among 10,000 women on combined HRT over a one-year period, there were 18 more cases of VTE, including 8 more cases of pulmonary embolism.[1]

In the *estrogen-alone* arm of the WHI trial, among 10,000 women on estrogen therapy over a one-year period, there were 7 more cases of VTE, although there was no statistically significant difference in the rate of pulmonary embolism.[2]

Generally recognized risk factors for VTE include a personal history, a family history (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic predisposition), severe obesity (body mass index > 30 kg/m^2) and systemic lupus erythematosus. The risk of VTE also increases with age and smoking.

The risk of VTE may be temporarily increased with prolonged immobilization, major surgery or trauma. In women on HRT, attention should be given to prophylactic measures to prevent VTE following surgery. Also, patients with varicose veins should be closely supervised. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, hormone therapy should be discontinued immediately, given the risks of long-term disability or fatality.

If feasible, estrogens with or without progestins should be discontinued at least 4-6 weeks before major surgery which may be associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

Hepatic/Biliary/Pancreatic

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

Hepatic Hemangioma
Particular caution is indicated in women with hepatic hemangiomas as estrogen may cause an exacerbation of this condition.

Jaundice
Caution is advised in patients with a history of liver and/or biliary disorders. If cholestatic jaundice develops during treatment, the treatment should be discontinued and appropriate investigations carried out**.**

Liver Function Tests
Liver function tests should be done periodically in subjects who are suspected of having hepatic disease. For information on endocrine and liver function tests, see **Monitoring and Laboratory Tests.**

Liver Disorders
Patients who have or have previously had liver disorder such as liver adenoma should be closely supervised as this condition may recur or be aggravated during treatment with Activelle®.

Immune

Angioedema
Estrogen may induce or exacerbate symptoms of angioedema, in particular in women with hereditary angioedema.

Systemic Lupus Erythematosus
Particular caution is indicated in women with systemic lupus erythematosus, as HRT may cause an exacerbation of this condition.

Monitoring and Laboratory Tests
Before Activelle® is administered, the patient should have a complete physical examination including a blood pressure determination. Breasts and pelvic organs should be appropriately examined and a Papanicolaou smear should be performed. Endometrial biopsy should be done only when indicated. Baseline tests should include mammography, measurements of blood glucose, calcium, triglycerides and cholesterol, and liver function tests.

The first follow-up examination should be done within 3-6 months after initiation of treatment to assess response to treatment. Thereafter, examinations should be made at intervals at least once a year. Appropriate investigations should be arranged at regular intervals as determined by the physician**.**

The importance of regular self-examination of the breasts should be discussed with the patient.

Neurologic

Cerebrovascular Insufficiency

Patients who develop visual disturbances, classical migraine, transient aphasia, paralysis or loss of consciousness should discontinue medication.

Patients with a previous history of classical migraine and who develop a recurrence or worsening of migraine symptoms should be reevaluated.

Dementia
Available epidemiological data indicate that the use of combined *estrogen plus progestin* in women age 65 and over may increase the risk of developing probable dementia.

The Women's Health Initiative Memory Study (WHIMS), a clinical substudy of the WHI, was designed to assess whether postmenopausal hormone replacement therapy (oral *estrogen plus progestin* or oral *estrogen-alone*) reduces the risk of dementia in women aged 65 and over (age range 65-79 years) and free of dementia at baseline.[6,7]

In the *estrogen plus progestin* arm of the WHIMS (n=4532), women with intact uteri were treated with daily 0.625 mg conjugated equine estrogens (CEE) plus 2.5 mg medroxyprogesterone acetate (MPA) or placebo for an average of 4.05 years. The results, when extrapolated to 10,000 women treated over a one-year period showed:

- 23 more cases of probable dementia (45 on combined HRT versus 22 on placebo).[6]

In the *estrogen-alone* arm of the WHIMS (n=2947), women with prior hysterectomy were treated with daily 0.625 mg CEE or placebo for an average of 5.21 years. The results, when extrapolated to 10,000 women treated over a one-year period showed:

- 12 more cases of probable dementia (37 on *estrogen-alone* versus 25 on placebo), although this difference did not reach statistical significance.[7]

When data from the *estrogen plus progestin* arm of the WHIMS and the *estrogen-alone* arm of the WHIMS were combined, as per the original WHIMS protocol, in 10,000 women over a one-year period, there were:

- 18 more cases of probable dementia (41 on *estrogen plus progestin* or *estrogen-alone* versus 23 on placebo).[7]

Epilepsy
Particular caution is indicated in women with epilepsy, as estrogens with or without progestins may cause an exacerbation of this condition.

Ophthalmologic
See 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS – **Neurologic**.

Renal

Fluid Retention
Estrogens with or without progestins may cause fluid retention. Therefore, particular caution is indicated in cardiac or renal dysfunction or asthma. If, in any of the above-mentioned conditions, a worsening of the underlying disease is diagnosed or suspected during treatment, the benefits and risks of treatment should be re-assessed based on the individual case**.**

Reproductive Health
See 7.1 Special Populations.

7.1 Special Populations

7.1.1 Pregnant Women

Activelle® is contraindicated during pregnancy.

If pregnancy occurs during medication with Activelle®, treatment should be withdrawn immediately.

Data on a limited number of exposed pregnancies indicate adverse effects of norethindrone on the fetus. At doses higher than normally used in Oral Contraceptives (OC) and HRT formulations masculinisation of female fetuses was observed.

The results of most epidemiological studies to date relevant to inadvertent fetal exposure to combinations of estrogens and progestins indicate no teratogenic or fetotoxic effect.

7.1.2 Breast-feeding

Activelle® is contraindicated when breastfeeding.

7.1.3 Pediatrics

Activelle® is not indicated for use in a pediatric population. Safety and effectiveness in pediatric patients have not been established.

7.1.4 Geriatrics

Geriatrics (> *65* years of age): Experience in treating women older than 65 years is limited.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

See 7 WARNINGS AND PRECAUTIONS regarding potential induction of malignant neoplasms and adverse effects similar to those of oral contraceptives.

The following adverse reactions have been reported with other estrogen/progestin combinations in general:

Blood and Lymphatic System Disorders
Altered coagulation tests (see 7 WARNINGS AND PRECAUTIONS, 9.7 Drug-Laboratory Test Interactions)

Cardiac Disorders
Palpitations; increase in blood pressure (see 7 WARNINGS AND PRECAUTIONS); coronary thrombosis

Endocrine Disorders
Increased blood sugar levels; decreased glucose tolerance

Eye Disorders
Neuro-ocular lesions (e.g. retinal thrombosis, optic neuritis); visual disturbances; steepening of the corneal curvature; intolerance to contact lenses

Gastrointestinal Disorders
Nausea; vomiting; abdominal discomfort (cramps, pressure, pain, bloating)

General Disorders and Administration Site Conditions
Fatigue; changes in appetite; changes in body weight; change in libido

Hepatobiliary Disorders
Gallbladder disorder; asymptomatic impaired liver function; cholestatic jaundice

Musculoskeletal and Connective Tissue Disorders
Musculoskeletal pain including leg pain not related to thromboembolic disease (usually transient, lasting 3-6 weeks) may occur

Nervous System Disorders
Aggravation of migraine episodes; headaches; dizziness; neuritis

Psychiatric Disorders
Mental depression; nervousness; irritability

Renal and Urinary Disorders
Cystitis; dysuria; sodium retention; edema

Reproductive System and Breast Disorders
Breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea; vaginal itching/discharge; dyspareunia; endometrial hyperplasia; pre-menstrual-like syndrome; reactivation of endometriosis; changes in cervical erosion and amount of cervical secretion; breast swelling and tenderness

Skin and Subcutaneous Tissue Disorders
Chloasma or melasma, which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism and acne

Vascular Disorders
Isolated cases of: thrombophlebitis; thromboembolic disorders

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

Adverse events reported by investigators in the Activelle® Phase 3 studies regardless of causality assessment are shown in Table 1 below.

Table 1 - All Treatment-Emergent Adverse Events Regardless of Relationship Reported at a Frequency of ≥ 1% with Activelle®

	Activelle® (n=371)	Placebo (n=82)
BODY AS A WHOLE – GENERAL DISORDERS		
Back Pain	5.7%	3.7%
Abdominal Pain	4.0%	-[1]
Pain NOS	3.8%	4.9%
Hot Flushes	3.5%	4.9%
Fatigue	2.2%	1.2%
Influenza-like symptoms	1.6%	1.2%
Allergic reaction	1.3%	-[1]
Chest Pain	1.3%	1.2%
Edema Peripheral	1.3%	-[1]
Leg Pain	1.1%	2.4%
CARDIOVASCULAR DISORDERS, GENERAL		
Hypertension	1.9%	4.9%
CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS		
Headache	15.6%	11.0%
Dizziness	1.1%	1.2%
Paraesthesia	1.1%	-[1]
GASTRO-INTESTINAL SYSTEM DISORDERS		
Nausea	4.9%	-[1]
Flatulence	3.8%	3.7%
Diarrhea	3.5%	1.2%
Constipation	2.7%	3.7%
Abdominal Pain	2.4%	2.4%
Dyspepsia	2.4%	3.7%
Gastroenteritis	2.2%	2.4%
Vomiting	1.1%	-[1]
HEARING AND VESTIBULAR DISORDERS		
Ear disorder NOS	1.1%	-[1]
METABOLIC AND NUTRITIONAL DISORDERS		
Weight increase	1.1%	3.7%
MUSCULO-SKELETAL SYSTEM DISORDERS		
Arthralgia	4.3%	3.7%
Fracture bone	2.2%	2.4%
Myalgia	1.6%	-[1]
NEOPLASMS		
Uterine fibroid	4.9%	4.9%
Ovarian cyst	2.7%	4.9%
Cervical uterine polyp	2.4%	2.4%
Breast neoplasm benign female	1.3%	0.0%
PSYCHIATRIC DISORDERS		
Insomnia	4.9%	6.1%
Depression	3.8%	-[1]

	Activelle® (n=371)	Placebo (n=82)
Emotional lability	1.3%	-[1]
Nervousness	1.3%	1.2%
REPRODUCTIVE DISORDERS, FEMALE		
Breast pain female	22.9%	4.9%
Postmenopausal bleeding	6.2%	1.2%
Breast enlargement	3.2%	-[1]
Breast disorder NOS	3.0%	1.2%
Abdominal pain	2.2%	1.2%
Cervical smear test positive	2.2%	-[1]
Leukorrhea	1.6%	2.4%
Vaginitis	1.1%	2.4%
RESISTANCE MECHANISM DISORDERS		
Infection NOS	2.2%	1.2%
Infection viral	3.8%	4.9%
Moniliasis genital	3.8%	-[1]
RESPIRATORY SYSTEM DISORDERS		
Upper respiratory tract infection	17.0%	13.4%
Sinusitis	8.1%	6.1%
Bronchitis	3.2%	1.2%
Rhinitis	2.7%	1.2%
Pharyngitis	1.9%	2.4%
Coughing	1.3%	2.4%
SECONDARY TERMS		
Injury accidental	5.9%	2.4%
Other evens	5.1%	2.4%
Cyst NOS	2.2%	1.2%
SKIN AND APPENDAGES DISORDERS		
Rash	2.2%	2.4%
Pruritus genital	1.6%	-[1]
Acne	1.3%	1.2%
Pruritus	1.1%	2.4%
URINARY SYSTEM DISORDERS		
Hematuria	1.1%	1.2%
Urinary tract infection	1.1%	2.4%

1. No adverse events reported

The most frequently reported adverse events in the clinical trials regardless of relationship to Activelle® were breast pain / tenderness (22.9%), upper respiratory tract infection (17.0%) and headache (15.6%).

There were no significant changes in mean body weight from baseline to the end of the trial (3 months or 12 months) in any Activelle® study**.**

8.3 Less Common Clinical Trial Adverse Reactions

Gastrointestinal: Abdominal distension
Immune System: Hypersensitivity

Metabolism and Nutrition: Fluid retention
Musculoskeletal, Connective Tissue and Bone: Leg cramps
Nervous System Disorders: Migraine
Skin and Subcutaneous Tissue Disorders: Alopecia
Vascular Disorders: Thrombophlebitis superficial/deep; pulmonary embolism

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

None of the observed changes with regard to hematology and clinical chemistry in clinical studies of Activelle® were clinically relevant.

8.5 Post-Market Adverse Reactions

Cardiac Disorders: Myocardial infarction

Eye Disorders: Visual disturbances

Gastrointestinal Disorders: Dyspepsia, vomiting

Hepatobiliary Disorders: Gallbladder disease, gallstones, cholelithiasis, cholelithiasis aggravated, cholelithiasis recurrence

Immune System Disorders: Generalized hypersensitivity reactions (e.g. anaphylactic reaction/shock)

Musculoskeletal and Connective Tissue Disorders: Leg cramps

Neoplasm Benign and Malignant: Endometrial cancer, uterine fibroid

Nervous System Disorders: Dizziness, stroke

Other: Weight decreased, blood pressure increased

Psychiatric Disorders: Insomnia, anxiety, libido decreased, libido increased

Reproductive System and Breast Disorders: Endometrial hyperplasia, vulvovaginal pruritus

Skin and Subcutaneous Tissue Disorders: Seborrhea, rash, angioneurotic edema, vascular purpura

Vascular Disorders: Hypertension aggravated

<u>If adverse symptoms persist, the prescription of HRT should be re-considered.</u>

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Estrogens are partially metabolized by cytochrome P450 3A4 (CYP3A4) as shown *in vitro* and *in vivo* studies. Therefore, estrogen drug metabolism may be affected by inducers or inhibitors of CYP3A4.

9.3 Drug-Behavioural Interactions

None identified.

9.4 Drug-Drug Interactions

Table 2 - Established or Potential Drug-Drug Interactions

Drug Class	Effect	Clinical comment
Anticonvulsants (e.g. phenobarbital, hydantoin, phenytoin, carbamazepine)	Reduce plasma concentrations of estrogens	Therapeutic monitoring is recommended
Anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz)	Reduce plasma concentrations of estrogens	Therapeutic monitoring is recommended
Protease inhibitors (e.g. ritonavir, telaprevir, nelfinavir)	Reduce plasma concentrations of estrogens	Therapeutic monitoring is recommended
Imidazoles (e.g. ketoconazole)	Increase plasma concentration of estrogens	Therapeutic monitoring is recommended
Barbiturates	Induce liver enzymes, may interfere with activity of orally administered estrogens	Therapeutic monitoring is recommended
Anticoagulants	Estrogens may diminish effectiveness	Therapeutic monitoring is recommended
Antidiabetics	Estrogens may diminish effectiveness	Therapeutic monitoring is recommended
Antihypertensives	Estrogens may diminish effectiveness	Therapeutic monitoring is recommended

9.5 Drug-Food Interactions

A single dose-study in 24 healthy postmenopausal women was conducted to investigate any potential impact of administration of Activelle® with and without food.

Administration of Activelle® with food did not modify the bioavailability of E_2, although food increased AUC_{0-72} for NET by 19% and decreased C_{max} for NET by 36%.

Grapefruit juice may increase plasma concentrations of estrogen.

9.6 Drug-Herb Interactions

It was found that some herbal products (e.g. St. John's Wort) which are available as over-the-counter (OTC) products might interfere with steroid metabolism, and therefore alter the efficacy and safety of estrogen/progestin products.

Physicians and other health care providers should be aware of other non-prescription products concomitantly used by the patient, including herbal and natural products, obtained from the

widely spread health stores.

9.7 Drug-Laboratory Test Interactions

The results of certain endocrine and liver function tests may be affected by estrogen-containing products:

- increased sulfobromophthalein retention;
- increased prothrombin time and partial thromboplastin time; increased levels of fibrinogen and fibrinogen activity; increased coagulation factors VII, VIII, IX, X; increased norepinephtrine-induced platelet aggregability; decreased antithrombin III;
- increased thyroxin-binding globulin (TBG), leading to increased circulating total thyroid hormone (T_4) as measured by column or radioimmunoassay; free T_3 resin uptake is decreased, reflecting the elevated TBG; free T_4 concentration is unaltered;
- other binding proteins may be elevated in serum (eg, corticosteroid binding globulin (CBG), sex-hormone binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively; free or biologically active hormone concentrations are unchanged;
- impaired glucose tolerance;
- increased serum triglycerides and phospholipids concentration

The results of the above laboratory tests should not be considered reliable unless therapy has been discontinued for two to four weeks.

The pathologist should be informed that the patient is receiving hormone replacement therapy when relevant specimens are submitted.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Estradiol: The active ingredient, synthetic estradiol, is chemically and biologically identical to endogenous human estradiol.

Estradiol, E2, is the major estrogenic hormone secreted by the human ovary. Among numerous effects, E2 is responsible for the development and maintenance of the female reproductive system and of secondary sexual characteristics. It promotes growth and development of the vagina, uterus, fallopian tubes and breasts. E2 contributes to the shaping of the skeleton, to the maintenance of tone and elasticity of urogenital structures, to changes in the epiphyses of the long bones that allow for the pubertal growth spurt and its termination, to the growth of auxiliary and pubic hair, and to the pigmentation of the nipples and genitals. It also affects the release of pituitary gonadotropins**.**

After menopause, when the ovaries have ceased to function, only small amounts of E2 are still produced. E2 is produced in the body by the aromatisation of androstenedione to estrone, E1, and to a lesser extent, testosterone to estradiol. Estrone is transformed to estradiol by the enzyme 17ß-hydroxysteroid-dehydrogenase. Both enzymes prevail in fat, liver and muscle tissue**.**

Loss of ovarian E2 production after menopause can result in instability of thermoregulation causing hot flushes associated with sleep disturbance and excessive sweating; accelerated loss of bone matrix and mineral, resulting in osteoporosis; alterations in lipid metabolism and urogenital atrophy, causing dyspareunia and urinary incontinence.

Norethindrone acetate: Because estrogens promote the growth of the endometrium, unopposed estrogens increase the risk of endometrial hyperplasia and cancer. The addition of a progestin may reduce the estrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

Norethindrone acetate, NETA, is a potent progestin that essentially mimics the biological effects of progesterone. Tissue effects of NETA are dependent on prior estrogen stimulation, and progesterone receptors have been identified in all tissues containing estrogen receptors.

NETA induces protein synthesis and also reduces the number of estrogen and progesterone receptors, thereby limiting excessive growth stimulation of target tissues by estrogen. 17-hydroxysteroid-dehydrogenase, which locally oxidizes E2 to its weaker estrogenic metabolite estrone, is also produced by NETA**.**

One of the major targets of NETA is the uterus, where it induces secretory transformation of the estrogen-primed endometrium. Once transformation of the endometrium is completed, the estrogen-primed endometrium is shed resulting in a regular cyclical bleeding.

Continuous addition of NETA in addition to estradiol will result in maintenance of the endometrium in an atrophic state in most of the women. This regimen avoids monthly withdrawal bleeding.

10.2 Pharmacodynamics

Estrogen pharmacology
Estradiol, E_2, is chemically and biologically identical to the endogenous human hormone. It is the major estrogenic hormone secreted by the human ovary which is also produced in small quantities (<20 pg/mL) in the postmenopausal woman. Among numerous effects, E_2, is responsible for the development and maintenance of the female reproductive system and secondary sex characteristics. By a direct action, it causes growth and development of the uterus, fallopian tubes, and vagina. With other hormones, such as pituitary hormones and progesterone, it causes enlargement of the breasts through promotion of ductal growth, stromal development, and the accretion of fat.

E_2 is intricately involved with other hormones, especially progesterone, in the processes of the ovulatory menstrual cycle and pregnancy and affect the release of pituitary gonadotropins. It also contributes to the shaping of the skeleton, maintenance of tone and elasticity of urogenital structures, changes in the epiphyses of the long bone that allow for the pubertal growth spurt and its termination, and pigmentation of the nipples and genitals**.**

Estrogen replacement therapy acts through a negative feedback pathway to reduce elevated circulating levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) observed in postmenopausal women.

Progestin pharmacology
Norethindrone Acetate, NETA, is a progestin that essentially mimics the biological effects of progesterone. NETA enhances cellular differentiation and generally opposes the actions of estrogen, by decreasing estrogen receptor levels, increasing local metabolism of estrogen to less active metabolites, or by inducing gene products that blunt cellular responses to estrogen.

NETA exerts its effect in target cells by binding to specific progesterone receptors which interact with progesterone response elements in target genes. Progesterone receptors have been identified in the female reproductive tract, breast, pituitary, hypothalamus and central nervous system. NETA produces similar endometrial changes to those of the naturally occurring hormone progesterone.

Unopposed estrogen therapy in women with intact uteri is associated with an increased risk of endometrial hyperplasia and endometrial carcinoma. The concomitant use of an appropriate dose of a progestin for an adequate time period reduces the incidence of endometrial hyperplasia and carcinoma in women with intact uteri who are receiving estrogen replacement therapy.

10.3 Pharmacokinetics

Table 3 - Pharmacokinetic Parameters of Activelle® after Single Dose

Component / metabolite	1 mg E_2/ 0.5 mg NETA Arithmetic Mean SD n=25
17β-estradiol (E_2)[1]	
AUC (pg/ml*h)	706 ± 252
C_{max} (pg/ml)	29.7 ± 9.4
t_{max} (h)	6.8 ± 2.9
$t_{½}$ (h)	13.2 ± 4.7
Estrone (E_1) [1]	
AUC (pg/ml*h)	3741 ± 1446
C_{max} (pg/ml)	230 ± 89
t_{max} (h)	5.7 ± 1.4
$t_{½}$ (h)	12.2 ± 4.6
Norethindrone (NET)	
AUC (pg/ml*h)	23681 ± 9023 (n=24)
C_{max} (pg/ml)	5308 ± 1510
t_{max} (h)	1.0 ± 0.0
$t_{½}$ (h)	11.4 ± 2.7

1. baseline adjusted

Absorption
E2 is well absorbed through the gastrointestinal tract. When given orally, E2 is extensively metabolized (first pass effect) to estrone sulfate. E2 circulates bound to sex-hormone-binding globulin (SHBG) (37%) and to albumin (61%), while only approximately 1-2% is unbound. The half-life of E2 is about 12-14 hours following single administration. See Table 3.

Distribution
After oral administration NETA (norethindrone acetate) is rapidly absorbed and transformed to norethindrone (NET). The terminal half-life of NET is about 8-11 hours. NET binds to SHBG (36%) and albumin (61%).

Metabolism
Metabolism of E2, occurs mainly in the liver and gut but also in target organs. Complex metabolic processes result in a dynamic equilibrium of circulating conjugated and unconjugated

estrogenic forms which are continually interconverted, especially between E_1 and E_2 and between esterified and nonesterified forms.

Elimination
A significant proportion of the circulating estrogen exists as a circulating reservoir for the formation of more active estrogenic species. A certain proportion of the estrogen is excreted into the bile and then reabsorbed from the intestine. During this enterohepatic recirculation, estrogens are desulfated and resulfated and undergo thorough conversion to less active estrogens (estriol and other estrogens), oxidation to nonestrogenic substances (catecholestrogens, which interact with catecholamine metabolism, especially in the central nervous system), and conjugation with glucuronic acids (which are then rapidly excreted in the urine).

Following oral administration of Activelle®, a peak plasma concentration is reached within 5-8 hours. The most important metabolites of norethindrone are isomers of 5α-dihydro-NET and of tetrahydro-NET, which are excreted mainly in the urine as sulfate or glucuronide conjugates. NETA undergoes first-pass metabolism in the liver and other enteric organs, and reaches a peak plasma concentration within 0.5-1.5 hours.

The pharmacokinetics of estradiol are not influenced by NET.

Special Populations and Conditions

- **Pediatrics:** Activelle® is not indicated for use in pediatric populations. Safety and effectiveness in pediatric patients have not been established.

- **Geriatrics:** Experience in treating women older than 65 years is limited. The pharmacokinetics in the elderly has not been studied.

- **Sex:** Activelle® is not indicated for use in male population.

- **Genetic Polymorphism**: No specific information available.

- **Ethnic Origin:** No specific information available.

- **Hepatic Insufficiency:** No specific information available.

- **Renal Insufficiency:** No specific information available.

11 STORAGE, STABILITY AND DISPOSAL

Keep out of reach of children. Store in a dry place, protected from light. Store between 15º-25º C. Do not refrigerate.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance: 17ß-estradiol

Non-proprietary name of the drug product: Estradiol (hemihydrate) USP/Ph.Eur.

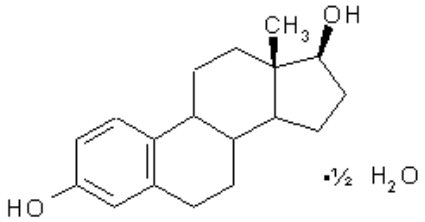
Chemical name:

1. 17ß-estradiol ½ H_2O
2. Estra-1, 3, 5 (10)-triene, 3, 17ß-diol

hemihydrate

Molecular formula and molecular mass: $C_{18}H_{24}O_2$
281.4

Structural formula:



Physicochemical properties:

Description: White or almost white crystalline powder

Solubility: Practically insoluble in water. 5.0 x 10^{-3} g/L

Melting point: 173 - 179°C

pKa: 10.71

n-octanol/water partition coefficient: log P_{OW} =3.30

Drug Substance: Norethindrone acetate

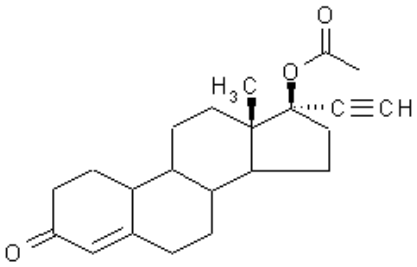
Non-proprietary name of the drug product: Norethindrone acetate USP/Ph. Eur.

Chemical name:

1. 19-Norpregn-4-en-20-yn-3-one, 17-(acetyloxy)-, (17α)
2. 17-Hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one acetate

Molecular formula and molecular mass: $C_{22}H_{28}O_3$
340.5

Structural formula:



Physicochemical properties:

Description:	White to yellowish-white crystalline powder
Solubility:	Practically insoluble (USP definition) in water
Melting point:	161 - 162°C
pKa:	The highest pKa value of NETA protonated at the conjugated ketone group in position 3 was calculated as -5, and the lowest pKa value of the neutral molecule was calculated as 19.

n-octanol/water partition coefficient: log P_{OW} = 3.67.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Effects on Menopausal Symptoms

Study demographics and trial design

A 12 week clinical trial, KLIM/PD/9/USA, was conducted to evaluate the efficacy of Activelle® in relief of moderate to severe vasomotor symptoms. The effects of both E_2 (N =29) alone and Activelle® (N = 29) when compared to placebo (N = 34) were apparent after the initial weeks of therapy. A significantly ($p<0.05$) larger reduction in the number and severity of hot flushes was observed for Activelle® compared to 1 mg E_2 after 4 weeks of treatment and throughout the remaining trial period (Figure 1). Thus, the addition of 0.5 mg NETA enhanced the reduction of vasomotor symptoms associated with 1 mg E_2.

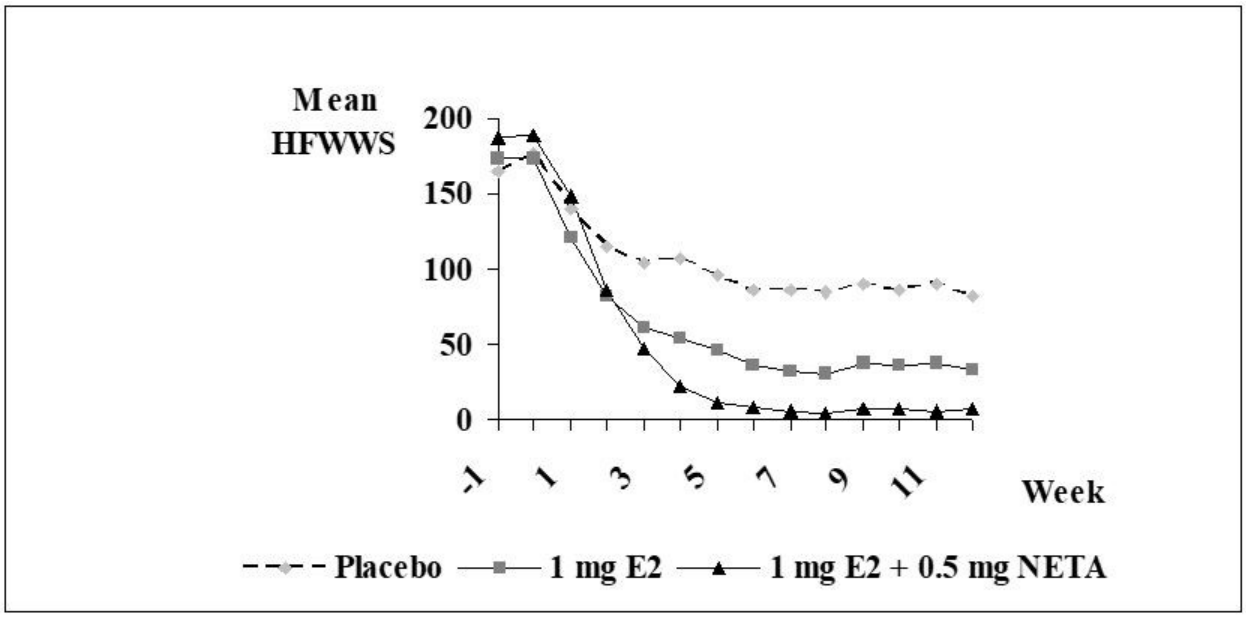


Figure 1: Effect of Activelle® on vasomotor symptoms as measured by a composite score of # and severity of hot flushes

Efficacy was assessed in terms of the weekly hot flush weighted score, weekly frequency of moderate and severe hot flushes, the occurrence of other menopausal symptoms, and menopausal symptoms recorded using the Greene Climacteric Scale.

In this trial, Activelle® was able to provide an adequate response in 89% of the women after 12 weeks of treatment (Figure 2). The number of women obtaining adequate relief with Activelle® was higher than that observed with 1 mg E_2.

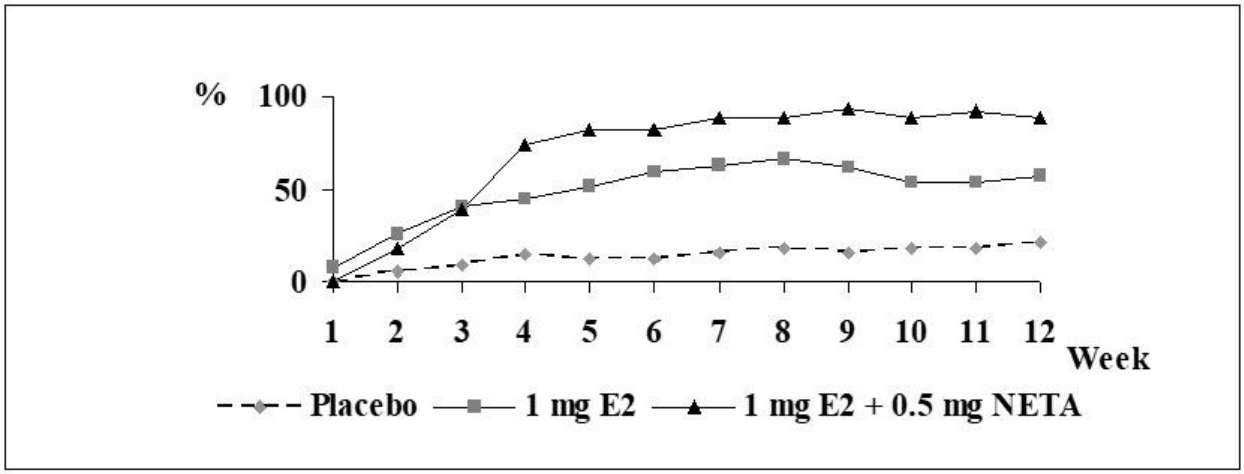


Figure 2: Percentage of women achieving at least a 90% reduction in vasomotor symptoms as measured by a composite score of # and severity of hot flushes

Throughout the clinical trials, Activelle® was associated with a high degree of adherence to treatment, as 95% of the women remained on treatment in placebo-controlled trials of 3 to 12 months duration. In the placebo-controlled trials, the rate of discontinuation due to adverse events was similar in the Activelle® group (2%) and the placebo group (4%).

Study KLIM/PD/9/USA evaluated estradiol 1 mg alone or in combination with NETA 0.5 mg in 92 menopausal women. This was 3 months prospective randomized, placebo-controlled, double-blind, multi-center, parallel-group trial to evaluate the efficacy and safety of treatment with 1 mg E2 and 1 mg E2 + 0.5 mg NETA for the relief of vasomotor hot flushes, as assessed by patients, when compared to placebo treatment. Patients were randomly assigned to a single daily dose of one of the three treatment groups and returned every 4 weeks for evaluation. The subjects were generally healthy menopausal women 40 to 60 years of age, with an intact uterus.

Study KLIM/PD1/N was a multi-centre, double-blind, randomized controlled efficacy trial of 12 weeks duration preceded by a 2 week run-in period and including 119 patients. Subjects were healthy, menopausal women 45 to 65 years of age, with amenorrhea for ≥ 3 months, who spontaneously complained of sweating and hot flushes. Subjects were randomized to one of the two arms of the trial 1mg E2 + 0.25 mg NETA or 1 mg E2 + 0.5 mg NETA. This trial compared climacteric symptoms of the two combination doses of E2 and NETA respectively and with placebo.

Study results

Effects on Menopausal Symptoms

The results of clinical studies indicate that the estrogen component of Activelle® substitutes for the loss of estrogen production in menopausal and postmenopausal women occurring in naturally or surgically induced estrogen deficiency states, and thus alleviates vasomotor symptoms. A dose finding study evaluated E_2 alone for symptom relief and it was concluded that both 1 and 2 mg of E_2 are effective while 1 mg of E_2 is the optimum dose.

During the trial, KLIM/PD/1/N, a statistical decrease in the number of severe, moderate and mild hot flushes were reported in the active treatment groups. Efficacy in reducing vasomotor symptoms was demonstrated at 4 weeks of treatment, reaching and almost complete reduction in the score by week 8. Menopausal symptoms were improved as shown with the decrease in Kupperman Menopausal Index, and by the Visual Analog Scales. No statistically significant differences were seen between active treatment groups in any of the bleeding parameters. Better bleeding control was observed with Activelle® than with 1 mg E2 + 0.25 mg NETA.

Effects on Endometrium

A pivotal study, KLIM/PD/7/USA**,** was designed to identify the lowest effective dose of NETA (0.1 or 0.25 mg) to be used in combination with 1 mg E2 that will substantially reduce the incidence of endometrial hyperplasia when compared with 1 mg E2 treatment alone. The uterine bleeding profile and the endometrium histology were assessed in this trial as well. This was a 12 month double-blind, randomized, parallel group, multicenter, dose finding study of 1,176 postmenopausal women. Subjects underwent a 4 week screening period followed by 12 months active treatment. Therapy consisted of a single daily dose of either 1 mg E2 with no norethindrone acetate or a combination of 1 mg of E2 and 0.1 mg, 0.25mg or 0.5 mg of NETA. The subjects' mean age range was 44 to 82 years of age.

The progestin component of Activelle®, norethindrone acetate (NETA), protects against the estrogen-induced proliferative changes in the endometrium. Long-term studies with Activelle® have documented that NETA when given concomitantly with E_2 reduces the incidence of endometrial hyperplasia associated with unopposed estrogen therapy.

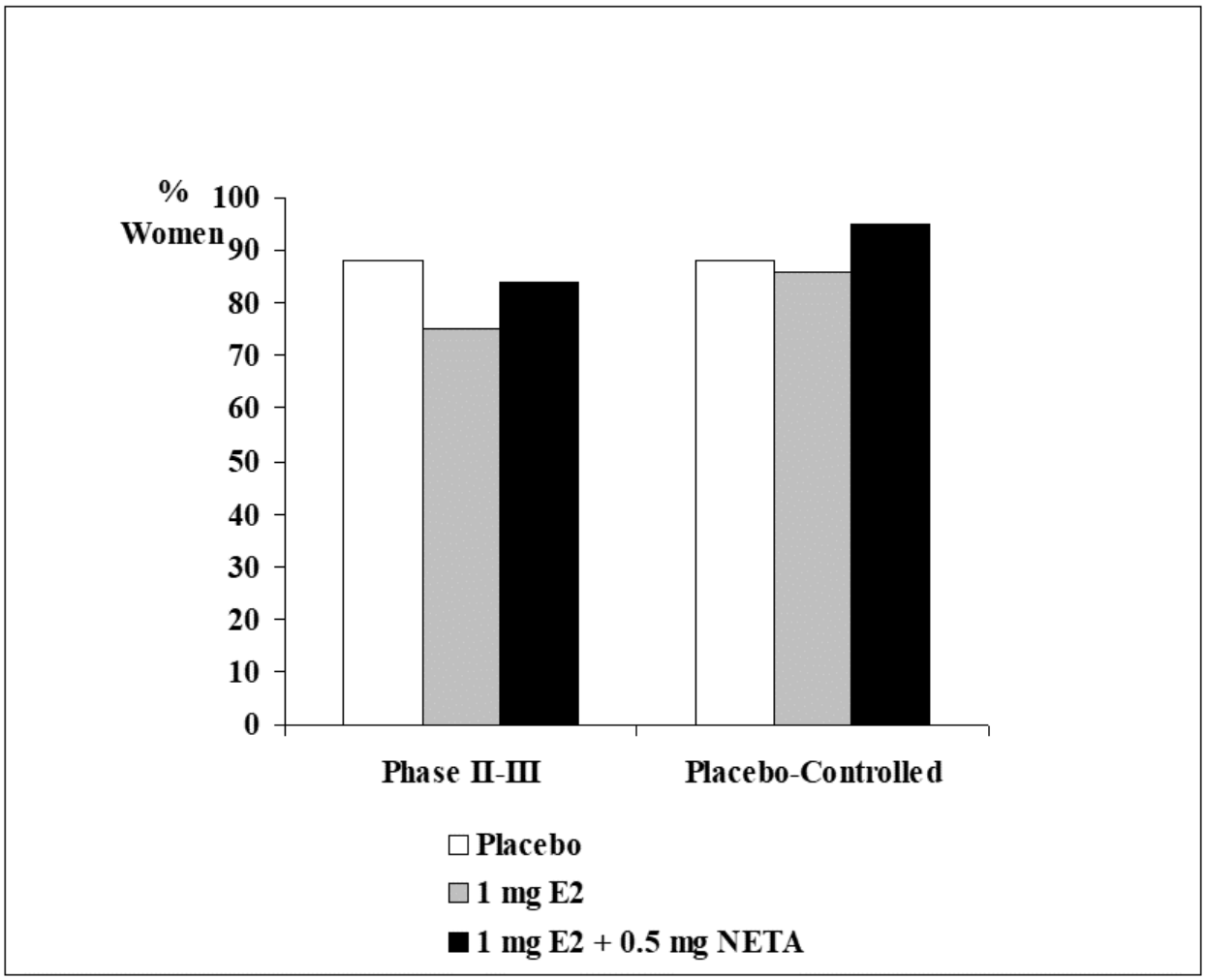


Figure 3: Completion Rates in Clinical Trials.

Effects on the Endometrium

The following table summarizes the incidence of endometrial hyperplasia after long term treatment with 1 mg E_2 unopposed versus Activelle® treatment in clinical trials of postmenopausal women. The incidence of endometrial hyperplasia associated with unopposed E_2 (1 mg) was decreased significantly in patients treated with Activelle®.

Table 4 - Incidence of Endometrial Hyperplasia in a 12 Month Study

Patients	Dose Groups	
	Activelle®	Unopposed 1 mg E2
	1 mg E2/0.5 mg NETA	
Total number of patients	295	296
# patients with histology evaluations	241	247
N (%) with hyperplasia	1 (0.4%)[1]	36 (14.6%)

1. simple hyperplasia without atypia

Effects on bleeding

Use of a continuous combined Hormone Replacement Therapy (HRT) such as Activelle® avoids monthly withdrawal bleeding associated with sequential HRT regimens. Figures 4 and 5 summarize the percentage of women bleeding over time. Fifty percent of the women exposed to Activelle® for up to one year did not experience any bleeding or spotting.

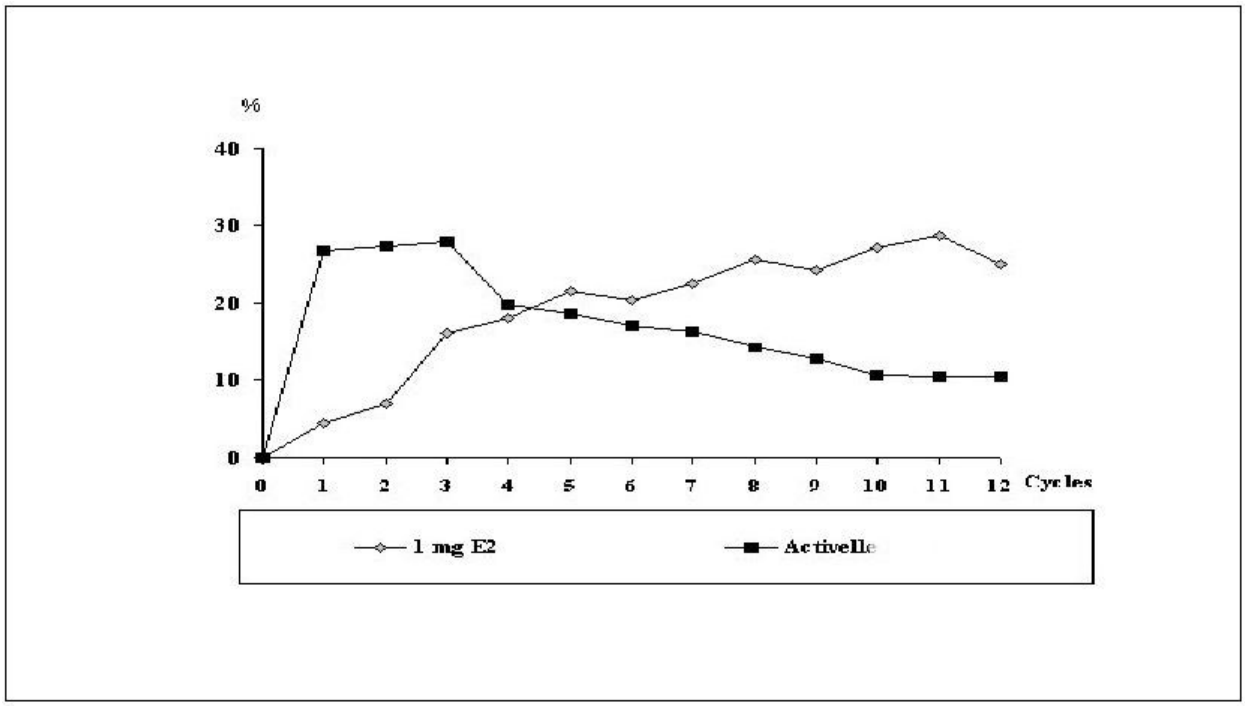


Figure 4: Incidence of bleeding or spotting over the 12 months treatment period.

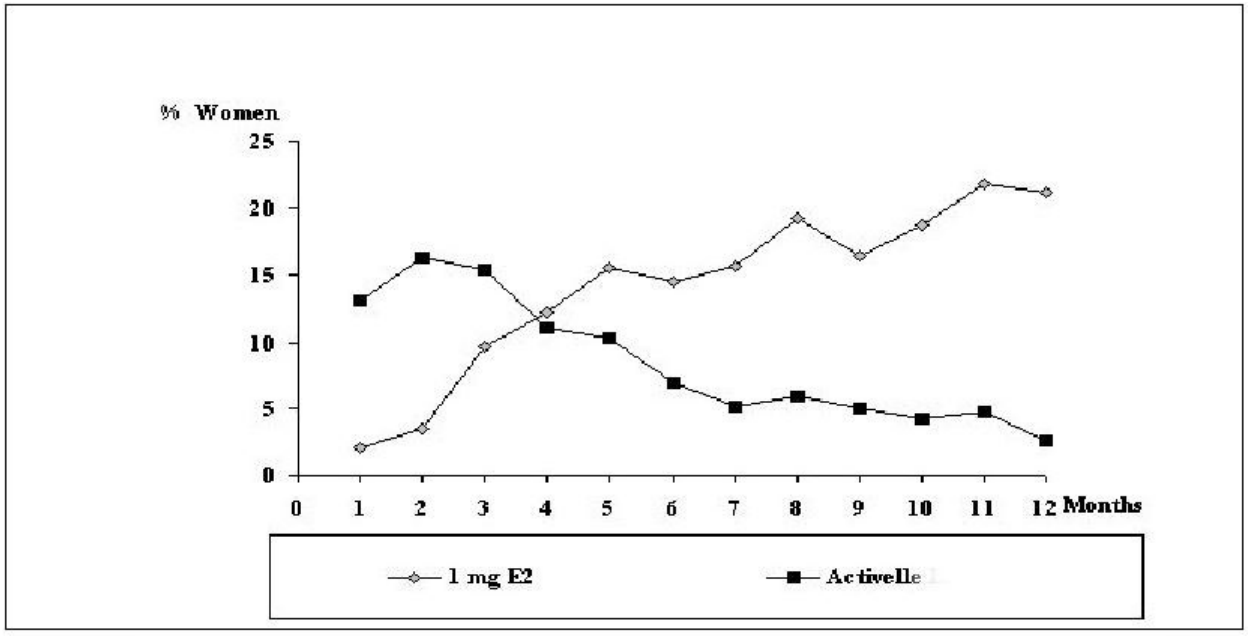
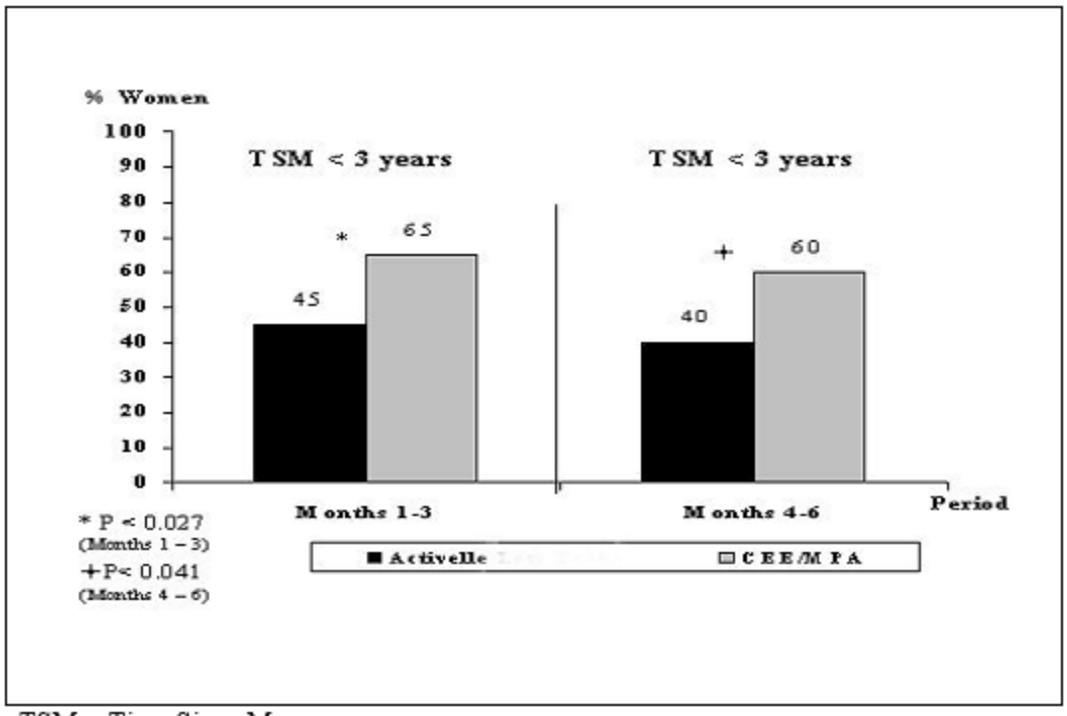


Figure 5: Incidence of bleeding (without spotting)

The incidence of bleeding with Activelle® is low, even during the initial months of treatment. Approximately 90% of the women were amenorrheic after 12 months of treatment. Of the remaining 10%, only 3% experienced bleeding and the remaining 7% spotting.

During the initial 3 months of therapy in a comparator trial, the frequency of women bleeding/spotting with Activelle® was significantly lower compared to that in those receiving continuous combined conjugated equine estrogens (CEE) 0.625 mg and medroxyprogesterone acetate (MPA) 2.5 mg. For women 1-3 years since last menses, the frequency of bleeding/spotting with Activelle® was significantly lower during 6 months of therapy than with CEE 0.625 mg and MPA 2.5 mg.



TSM = Time Since Menopause

Figure 6: Frequency of Women Bleeding/Spotting in Months 1-3 and Months 4-6

Lipid Effects

The effect of Activelle® on lipid and lipoprotein parameters in healthy postmenopausal women has been evaluated in double-blind, randomized, placebo-controlled trials of 3 to 24 months duration. A summary of the lipid and lipoprotein changes is displayed in Table 5.

Activelle® significantly decreases total cholesterol and LDL-cholesterol compared to placebo. Activelle® does not increase triglycerides or VLDL-cholesterol. The decrease in total cholesterol observed with E2 alone is not attenuated but rather enhanced by the addition of NETA. In addition, NETA blunts or reverses the estradiol-induced raise of triglycerides.

HDL-cholesterol either does not change with Activelle®, or decreases significantly when compared to baseline. However, the LDL/HDL ratio remains unchanged while it deteriorates significantly in the placebo group. Lipoprotein (a) has been found to decrease significantly after 12 months of treatment with Activelle®.

Treatment for 12 months with Activelle® did not modify apolipoprotein-A. A significant decrease in Apolipoprotein B has been reported after 6 and 12 months respectively of treatment with Activelle®.

Table 5 - Percent Change from Baseline in Lipid/Lipoprotein Parameters with Activelle® and Placebo

Parameter	Activelle® n = 35	Placebo n = 34
Total cholesterol	-10.5[1]	-0.8
LDL-cholesterol	-10.8[1]	0.8
HDL-cholesterol	-12.4[1]	-6.1*
VLDL-cholesterol	-0.1	4.6
Triglycerides	2.2	4.4
Apolipoprotein A	-0.6	1.6
Apolipoprotein B	-7.2[1]	-1.3
Lipoprotein (a)	-20.9[1]	-5.3
LDL:HDL Ratio	0.1	9.2

1. significantly ($p<0.05$) different from baseline

Hemostatic Changes

The effect of Activelle® in healthy postmenopausal women was evaluated in two placebo-controlled trials of 6 and 12 months duration.

Activelle® significantly decreases factor VII activity compared to placebo and unopposed estradiol. Combined E_2 and NETA appears to decrease factor VII activity. Fibrinogen is not modified during treatment with Activelle®; this is in contrast with the significant increase in fibrinogen observed with placebo.

Antithrombin III activity is significantly reduced following treatment with Activelle®. With regards to fibrinolytic parameters, plasminogen activator inhibitor-1 (PAI-1) is decreased after 12 months of treatment with Activelle®. No other changes have been reported in the hemostatic parameters assessed during Activelle® treatment.

A summary of the changes in hemostatic parameters assessed after 12 months of treatment with Activelle® is displayed in Table 6.

Table 6 - Percent Change from Baseline in Activelle® Compared to Placebo

Parameter	Activelle® n = 35	Placebo n = 34
Factor VII clotting activity	-23.1[1]	-4.0[1]
Fibrinogen	-3.7	12.4[1]
Antithrombin III activity	-9.8	-1.2
Plasminogen activator inhibitor-1 activity	-49.9[1]	2.6
Platelets	-0.9	-6.3

1. significantly ($p<0.05$) different from baseline

Glucose Metabolism

The effect of Activelle® on carbohydrate metabolism in healthy postmenopausal women was evaluated in 4 double-blind, randomized, placebo-controlled trials of 3, 6, 12 and 24 months duration.

Fasting glucose, insulin and c-peptide levels do not change following 6 or 12 months of treatment with Activelle®. There is no worsening of glucose tolerance with Activelle® as glucose and insulin responses to an oral glucose tolerance test, do not change during treatment. Insulin sensitivity was assessed in a 3-month placebo-controlled trial in which Activelle® did not change compared to placebo. Finally, glycemic control measured by HBA_{1c}, was found to improve with Activelle® compared to placebo.

15 MICROBIOLOGY

Not applicable.

16 NON-CLINICAL TOXICOLOGY

Due to physiological, pharmacokinetic and pharmacodynamic interspecies differences, quantitative extrapolation from animals to humans must be carried out with great caution. There is an extensive clinical experience with the use of E2 and NETA in humans and no effects can be predicted from animal toxicology findings other than those documented with human use.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrActivelle®

Estradiol and Norethindrone Acetate Tablets

Read this carefully before you start taking **Activelle®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Activelle®**.

Serious Warnings and Precautions

In postmenopausal women taking estrogen-alone, who had surgery to remove the uterus (called a hysterectomy), there is an increased risk of:

- stroke (bleeding or blot clot in the brain), and
- deep vein thrombosis (blood clots in the deep veins of the leg or arm).

Estrogens with progestin, like Activelle®, should:

- not be used to prevent heart disease or stroke.
- be used at the **lowest effective dose** and for the **shortest period of time** possible. You should have regular medical check-ups.

What is Activelle® used for?

Activelle® is used only in women who still have a uterus. It is used to treat the following conditions that can occur as a result of lower estrogen levels associated with menopause:

- moderate to severe vasomotor symptoms of menopause (such as hot flashes).
- changes in the vagina and/or external genitalia (vulva).

How does Activelle® work?

After menopause, your body makes less estrogen.

Activelle® is a Hormone Replacement Therapy (HRT) that contains 2 ingredients that have different functions. The estradiol (a type of estrogen) in Activelle® replaces the estrogen that some women are missing. This may help relieve your menopausal symptoms such as hot flashes. Since estrogen may also stimulate the lining of the uterus to grow Activelle® also contains the progestin hormone called norethindrone acetate (NETA). NETA helps to reduce the risk of overgrowth of the lining of the uterus (a condition called endometrial hyperplasia), which could lead to cancer of the lining of the uterus (womb).

What are the ingredients in Activelle®?

Medicinal ingredients: Estradiol, and norethindrone acetate.

Non-medicinal ingredients: Copovidone, hypromellose, lactose monohydrate, magnesium stearate, maize starch, talc, and triacetin.

Activelle® comes in the following dosage form(s):

Film-coated tablets: 1 mg estradiol (as estradiol hemihydrate) and 0.5 mg norethindrone acetate.

Do not use Activelle® if:

- you are allergic to estradiol, norethindrone acetate or to any of the ingredients in Activelle®,
- you have or have had liver problems, and the blood tests to measure how your liver is working have not returned to normal.
- you have or have had estrogen-dependent or progestin-dependent cancer (e.g. endometrial cancer).
- you have thickening of the lining of the uterus (endometrial hyperplasia).
- you have or have had breast cancer.
- you have unexpected or unusual vaginal bleeding.
- you are pregnant or think you might be pregnant.
- you are breast-feeding
- you have, or have had a heart attack, stroke, angina or heart disease
- you have or have had blood clotting problems such as:
    - deep vein thrombosis (where a blood clot forms in a deep vein);
    - pulmonary embolism (where a blood clot forms in the lung);
    - Thromboembolism (where a blood clot blocks the flow of blood through your veins).
- you have partial or complete loss of vision due to blood vessel disease of the eye (called ophthalmic vascular disease)
- you have porphyria (a disease caused by how your body makes heme – a component of your blood).
- you have migraine headaches.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Activelle®. Talk about any health conditions or problems you may have, including if you:

- have a history of allergy or intolerance to any medications or other substances.
- have a personal history of breast disease (including breast lumps) and/or breast biopsies, or a family history of breast cancer.
- have experienced any unusual or undiagnosed vaginal bleeding.
- have or had:
    - a history of uterine fibroids (growths) inside of your uterus;
    - endometriosis (growth of the uterine lining outside your uterus); and/or
    - a history of overgrowth of the lining of the uterus (endometrial hyperplasia)
- have a history of liver disease or liver tumors, jaundice (yellowing of the eyes and/or skin).
- have a history of itching related to estrogen use or during pregnancy.
- have a history of migraine headaches.
- have a history of high blood pressure.
- have a personal or family history of blood clots, or a personal history of heart disease or stroke.
- have a history of kidney disease.

- have asthma.
- have seizures (epilepsy).
- have gallbladder disease.
- have a history of bone disease (this includes certain metabolic conditions or cancers that can affect the calcium and phosphorus levels in your blood).
- have a condition where your thyroid gland fails to produce enough thyroid hormone (hypothyroidism) and you are being treated with thyroid hormone replacement therapy.
- have a condition called hereditary angioedema, or if you have had episodes of rapid swelling of the hands, feet, face, lips, eyes, tongue, throat (airway blockage) or digestive tract.
- have been diagnosed with lupus.
- have been diagnosed with diabetes.
- have or had high levels of fat in your blood (cholesterol, triglycerides).
- have been diagnosed with depression.
- will have to lie in bed for an extended period of time (prolonged bed rest).
- are pregnant or may be pregnant.
- are breastfeeding.
- have been diagnosed with hearing loss due to abnormal bone growth in your ear (otosclerosis).
- have an intolerance to lactose. Activelle® contains lactose.
- have eye problems.
- smoke.
- are having surgery.

Other warnings you should know about:

Breast cancer:

- There is a higher risk of breast cancer in postmenopausal women taking combined estrogen plus progestin.
- Estrogens with or without progestins should not be taken by women who have a personal history of breast cancer.
- Talk to your healthcare professional before starting HRT if you have:
    - a family history of breast cancer or breast lumps, breast biopsies or abnormal mammograms (breast x-rays)
    - never had a baby before or had your first full-term pregnancy at an older age
    - you are overweight
    - you started menstruating at an early age

Overgrowth of the lining of the uterus and cancer of the uterus:

- Taking estrogen-only therapy by postmenopausal women who still have a uterus increases your risk of excessive thickening of the lining of the womb (endometrial hyperplasia) and cancer of the lining of the womb (endometrial cancer).

- Talk to your healthcare professional about progestin therapy and risk factors for endometrial hyperplasia and endometrial cancer. You should also report any unexpected or unusual vaginal bleeding to your healthcare professional.

- If you have had your uterus removed, you are not at risk of developing endometrial hyperplasia or endometrial cancer. Progestin therapy is not generally required in women who have had a hysterectomy (surgical removal of the uterus).

Ovarian cancer: Taking HRT for 5 years or more increases your risk of developing ovarian cancer. Ovarian cancer may develop when using HRT with estrogen alone or estrogen in combination with progestin.

Abnormal Blood Clotting: Taking Activelle® can increase your risk of developing blood clots in your large veins. You should discuss risk factors for blood clots with your healthcare professional since blood clots can be life-threatening or cause serious disability. Talk to your healthcare professional if:

- you or a family member has had blood clots.
- you smoke.
- you are overweight.

The risk of blood clots is increased as you get older. It is also temporarily increased:
- if you are inactive for long periods of time.
- following major surgery.

If you are going to have surgery, your healthcare professional may recommend you temporarily stop take Activelle® about 4 to 6 weeks before the procedure to reduce the risk of blood clots.

Gallbladder Disease: Your risk of developing gallbladder disease that requires surgery is increased when taking estrogens.

Dementia: Your risk of developing dementia (memory loss) is increased if you are a woman aged 65 and over taking estrogen with progestin.

Check-ups and testing: You will have regular visits with your healthcare professional, before and during your treatment. They will:

- Do a physical exam and blood work (which may include a pregnancy test) before you begin treatment. Your visit may include a blood pressure check, a breast exam, a Pap smear and pelvic exam. You should have a mammogram before starting treatment and at regular intervals as recommended by your healthcare professional.

- Do regular follow-up exams including a breast exam and blood pressure check at least once a year to identify side effects associated with the use of Activelle®. Your first follow-up visit should be within 3 to 6 months of starting treatment.

- Advise you to regularly check your own breasts. Talk to your healthcare professional if you are unsure on the technique to use.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Activelle®:

- medicines used for the treatment of epilepsy (e.g. phenobarbital, hydantoin, phenytoin and carbamazepine).
- medicines used for tuberculosis (e.g. rifampicin, rifabutin).
- medicines used for the treatment of HIV or hepatitis infections (e.g. nevirapine, efavirenz, ritonavir, telaprevir and nelfinavir).
- medicines used for the prevention or treatment of blood clots (anticoagulant).
- medicines used to treat diabetes.
- medicines used to treat high blood pressure (antihypertensive).
- medicines used to help you relax such as barbiturates.
- herbal treatments to treat depression containing St. John's Wort (Hypericum perforatum).
- medicines used to treat fungal infection such as ketoconazole.
- Grapefruit juice.

How to take Activelle®:

- You may begin taking Activelle® on any day of the week that is convenient. If you are switching from another Hormone Replacement Therapy product, start Activelle® right after withdrawal bleeding (menstrual period) has ended.
- Your healthcare professional will prescribe the lowest dose to treat your symptoms for as short amount of time as necessary. Speak to your healthcare professional if you think your dose is too strong or not strong enough.
- Activelle® is not a contraceptive. If it is less than 12 months since your last menstrual period or you are under 50 years old, you may still need to use additional contraception to prevent pregnancy. Talk to your healthcare professional.

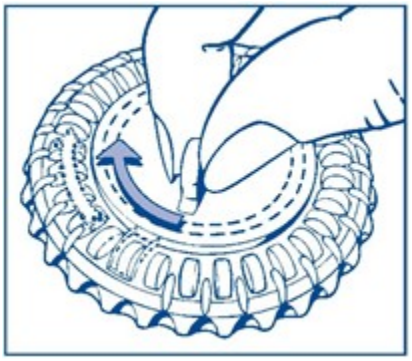
Usual dose:

Take 1 tablet once daily, at around the same time each day. Once you have finished all the 28 tablets in the pack, start a new pack without interruption.

How to use the dial pack:
Activelle® is supplied in calendar dial packs of 28 white tablets. Follow the steps below on how to use the calendar dial pack.

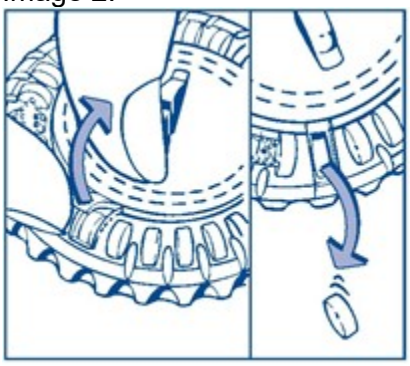
1. **Set the day reminder**
   Turn the inner disc to set the day of the week for the first tablet (see image 1). The day of the week should be aligned with the little plastic tab.

   Image 1:



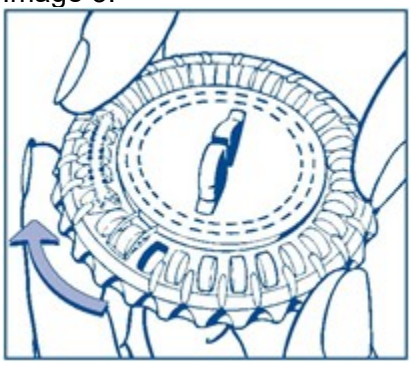
2. **How to take the first tablet**
   The first tablet to be taken is under the sealed opening in the transparent outer rim of the dial-pack. Break the plastic tab and tip out the first tablet (see image 2).

   Image 2:



3. **Following days**
   Move the outer transparent dial clockwise one space to the next day as indicated by the arrow (see image 3). Tip out the next tablet.

   Image 3:



   The transparent dial can only be turned after the tablet in the opening has been removed.

Overdose:

Signs of an overdose may include nausea, vomiting, breast discomfort, fluid retention (swelling), bloating, vaginal bleeding, depressed mood, tiredness, acne, and growth of body or facial hair.

If you think you, or a person you are caring for, have taken too much Activelle®, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

If you forget to take a tablet and it's within 12 hours of the time you should have taken it, take it as soon as you remember. If it has been more than 12 hours do not take this dose. The next dose should be taken at the normal time. Do not take two tablets to make up for the missed dose.

Forgetting a dose may increase the likelihood of breakthrough bleeding and spotting.

What are possible side effects from using Activelle®?

These are not all the possible side effects you may have when taking Activelle®. If you experience any side effects not listed here, tell your healthcare professional.

- Nausea, vomiting.
- Abdominal cramps, pressure, pain, and bloating.
- Feeling tired (fatigue), inability to sleep or stay awake.
- Changes in appetite, and body weight.
- Change in sex drive.
- Muscle aches and pains, including in the legs, abdominal, back, chest, and pelvic.
- Headache, dizziness.
- Anxiety, feeling nervous.
- Vaginal itching, discharge, discomfort, and odour.
- Pain during or after sex.
- Breast tenderness, pain, swelling.
- Skin darkening on the face (chloasma).
- Acne, itchy skin.
- Hair loss or abnormal hairiness.
- Hot flushes.
- Flu-like symptoms.
- Tingling sensation of the skin.
- Passing gas (flatulence).
- Diarrhea, constipation.
- Joint stiffness.

Activelle® can cause abnormal blood and positive cervical smear test results. Your healthcare professional will decide when to do these tests and will interpret the results.

Serious side effects and what to do about them			
	Talk to your healthcare professional		**Stop taking drug and get immediate medical help**
Symptom / effect	**Only if severe**	**In all cases**	
COMMON			

Serious side effects and what to do about them			
	Talk to your healthcare professional		Stop taking drug and get immediate medical help
Symptom / effect	**Only if severe**	**In all cases**	
Peripheral edema: Swelling of arms and legs		✓	
Depression (sad mood that won't go away): difficulty sleeping or sleeping too much, changes in appetite or weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family, gatherings and activities with friends, reduced libido (sex drive) and thoughts of death or suicide		✓	
Vaginitis: Genital infection with a fungus, vaginal inflammation, discharge, itching, and pain	✓		
UNCOMMON			
Allergic reaction: difficulty swallowing or breathing, wheezing; drop in blood pressure; feeling sick to your stomach and throwing up; hives or rash; swelling of the face, lips, tongue or throat.			✓
Erythema multiforme (an allergic skin reaction): raised red or purple skin patches, possibly with blister or crust in the center; possibly swollen lips, mild itching or burning			✓
Erythema nodosum (swelling of the fat cells under the skin): tender red lumps usually on both shins			✓
Vaginal bleeding changes: increased or decreased menstrual bleeding, spotting, infrequent periods or absence of bleeding, severe vaginal bleeding		✓	
Deep Vein Thrombosis (blood clot in the legs or arms): pain or swelling in the leg or arm			✓
Thromboembolism (blood clot in a vein or artery): pain or tenderness or swelling in your arm or leg, skin that is red or warm, coldness, tingling or numbness, pale skin, muscle pain or spasms, weakness			✓
Pulmonary Embolism (blood clot in the lungs): Sharp pain in the chest, coughing blood, sudden shortness of breath			✓

Serious side effects and what to do about them			
	Talk to your healthcare professional		Stop taking drug and get immediate medical help
Symptom / effect	**Only if severe**	**In all cases**	
Eye disorders: blurred vision, loss of vision in eye, increased sensitivity of the eyes to light, eye pain or redness, swelling and itching of the eyelids, decreased sharpness of vision, eye irritation, blocked eye veins		✓	
Stroke (bleeding or blood clot in the brain): sudden severe headache or worsening of headache, vomiting, dizziness, fainting, problems with your vision or speech, weakness or numbness in face, arm or leg			✓
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse or heart palpitations.		✓	
Migraine: severe headache often accompanied by nausea, vomiting and sensitivity to light	✓		
RARE			
Breast abnormalities (including breast cancer): dimpling or sinking of the skin, changes in the nipple, or any lumps you see or feel, discharge from breasts, enlarged breasts, swelling			✓
Coronary thrombosis (blocked heart arteries): chest pain and pressure, shortness of breath			✓
Cystitis (bladder infection): increased need to urinate, pain in the pelvis or lower back, frequent urination during the night, cloudy urine that may contain blood, burning sensation when passing urine		✓	
Endometrial hyperplasia (abnormal growth of the lining of the uterus): menstrual bleeding that is heavier or lasts longer than normal, bleeding after menopause, menstrual cycles that are shorter than 21 days			✓
Endometrial cancer (cancer of the lining of the uterus): vaginal bleeding not associated with a period or after menopause; abnormal blood-tinged discharge from the vagina; pain in the pelvis			✓

Serious side effects and what to do about them			
	Talk to your healthcare professional		Stop taking drug and get immediate medical help
Symptom / effect	Only if severe	In all cases	
Gallbladder problems: fever, nausea, pain that radiates to your shoulder or back, severe pain in your upper right abdomen, vomiting	✓		
Liver problems: yellowing of your skin and eyes (jaundice), right upper stomach area pain or swelling, nausea or vomiting, unusual dark urine, light coloured stool, unusual tiredness		✓	
Neuritis (inflammation of the nerve): pain, feeling of pins-and needles, numbness, loss of reflexes		✓	
Palpitations (fast-beating, fluttering or pounding heart): heart skipping beats, beating too fast, pounding, fluttering rapidly			✓
Urinary tract disorders: difficulty and pain when passing urine, blood in urine		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store at room temperature between 15°C - 25°C.
- Store in a dry place. Do not refrigerate.
- Protect from light by keeping the dial-pack inside the outer carton.
- Keep out of the reach and sight of children

If you want more information about Activelle®:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for health professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.novonordisk.ca; or by calling 1-800-465-4334.

This leaflet was prepared by Novo Nordisk Canada Inc.

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