

## PRODUCT MONOGRAPH

<sup>PR</sup>Activelle®

1 mg Estradiol  
0.5mg Norethindrone acetate

Film-coated tablets

Professed Standard

Estrogenic Hormones/Progestin

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# Activelle®

1 mg Estradiol  
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## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>Clinically Relevant Nonmedicinal Ingredients</b>
Oral	Film-coated tablet Estradiol 1mg (as hemihydrate) and norethisterone acetate 0.5mg	Lactose monohydrate <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

### INDICATIONS AND CLINICAL USE

Activelle® (1 mg Estradiol 0.5mg 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 progestogen to prevent endometrial hyperplasia.

### CONTRAINDICATIONS

- § Patients with known hypersensitivity to this drug or any ingredient in the formulation or components of the container. For complete listing, see the Dosage Forms, 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 or suspected 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
- § Lactation

## WARNINGS AND PRECAUTIONS

### 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.<sup>1-3</sup>

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.<sup>1</sup>

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.<sup>2</sup>

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.

### General

For the treatment of postmenopausal symptoms, 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).<sup>1</sup>

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.<sup>3</sup>

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.<sup>2</sup>

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 **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.

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 greatly 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])<sup>1</sup>. 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<sup>®</sup> 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<sup>®</sup> 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***

Recent epidemiologic studies have found the use of hormone replacement therapy (estrogen-alone and estrogen plus progestin therapies, in particular for five 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.<sup>1,4,5</sup> 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.<sup>1,2</sup>

### **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.<sup>2</sup>

### **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.<sup>4</sup>

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.<sup>5</sup>

### ***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**

Estrogens should be used with caution in patients with otosclerosis.

### **Endocrine and Metabolism**

#### ***Glucose and lipid metabolism***

A worsening of glucose tolerance and lipid metabolism have been observed in a significant percentage of peri- and post-menopausal 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: 1mg E2 (n=19) and 1mg E2 + 0.5mg NETA (n=19) showed no change over time in glycemic control as measured by fasting glucose, serum free insulin, HBA<sub>1c</sub> or fructosamine. In post menopausal women with type 2 diabetes after 6 months of treatment, diabetic women receiving Activelle<sup>®</sup> 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.

### ***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.

### ***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 **Drug-Laboratory Test Interactions**).

### ***Other Conditions***

Activelle<sup>®</sup> 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<sup>®</sup>. The patients should be closely monitored.

### **Gastrointestinal**

No specific information available.

### **Genitourinary**

#### ***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 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. If breakthrough bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.

### ***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.

### ***Endometriosis***

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

## **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 venous thromboembolism, including 8 more cases of pulmonary embolism.<sup>1</sup>

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 venous thromboembolism, although there was no statistically significant difference in the rate of pulmonary embolism.<sup>2</sup>

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<sup>2</sup>) 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 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.

### ***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<sup>®</sup>.

## **Immune**

### ***Systemic lupus erythematosus***

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

## **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.<sup>6,7</sup>

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).<sup>6</sup>

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.<sup>7</sup>

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).<sup>7</sup>

It is unknown whether these findings apply to younger postmenopausal women.

### ***Epilepsy***

Particular caution is indicated in women with epilepsy, as HRT may cause an exacerbation of this condition.

### **Ophthalmologic**

See **Contraindications and Warnings and Precautions – Neurologic**.

### **Psychiatric**

No specific information is available.

### **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 reassessed based on the individual case.

### **Respiratory**

No specific information available.

### **Sensitivity/Resistance**

See **Contraindications**.

### **Sexual Function/Reproduction**

See **Warnings and Precautions – Special Populations**.

### **Skin**

No specific information available.

### **Special Populations**

**Pregnant Women:** Activelle<sup>®</sup> is contraindicated during pregnancy.

If pregnancy occurs during medication with Activelle<sup>®</sup>, 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.

**Nursing Women:** Activelle<sup>®</sup> is contraindicated during lactation.

**Pediatrics:** Activelle<sup>®</sup> is not indicated for use in a pediatric population. Safety and effectiveness in pediatric patients have not been established.

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

### **Monitoring and Laboratory Tests**

Before Activelle<sup>®</sup> 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.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

See **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 **Warnings and Precautions, Drug-Laboratory Tests Interactions**).

#### **Cardiac disorders**

Palpitations; increase in blood pressure (see **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.

### **Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Adverse events reported by investigators in the Activelle<sup>®</sup> 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  $\geq 1\%$  with Activelle<sup>®</sup>**

	Activelle (n=371)	Placebo (n=82)
<b>BODY AS A WHOLE – GENERAL DISORDERS</b>		
Back Pain	5.7%	3.7%
Abdominal Pain	4.0%	-*
Pain NOS	3.8%	4.9%
Hot Flashes	3.5%	4.9%
Fatigue	2.2%	1.2%
Influenza-like symptoms	1.6%	1.2%
Allergic reaction	1.3%	-*
Chest Pain	1.3%	1.2%
Oedema Peripheral	1.3%	-*
Leg Pain	1.1%	2.4%
<b>CARDIOVASCULAR DISORDERS, GENERAL</b>		
Hypertension	1.9%	4.9%
<b>CENTR &amp; PERIPH NERV SYST DISORDERS</b>		
Headache	15.6%	11.0%
Dizziness	1.1%	1.2%
Paraesthesia	1.1%	-*
<b>GASTRO-INTESTINAL SYSTEM DISORDERS</b>		
Nausea	4.9%	-*
Flatulence	3.8%	3.7%
Diarrhoea	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%	-*
<b>HEARING AND VESTIBULAR DISORDERS</b>		

	Activelle (n=371)	Placebo (n=82)
Ear disorder NOS	1.1%	-*
<b>METABOLIC AND NUTRITIONAL DISORDERS</b>		
Weight increase	1.1%	3.7%
<b>MUSCULO-SKELETAL SYSTEM DISORDERS</b>		
Arthralgia	4.3%	3.7%
Fracture bone	2.2%	2.4%
Myalgia	1.6%	-*
<b>NEOPLASMS</b>		
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%
<b>PSYCHIATRIC DISORDERS</b>		
Insomnia	4.9%	6.1%
Depression	3.8%	-*
Emotional lability	1.3%	-*
Nervousness	1.3%	1.2%
<b>REPRODUCTIVE DISORDERS, FEMALE</b>		
Breast pain female	22.9%	4.9%
Post-menopausal bleeding	6.2%	1.2%
Breast enlargement	3.2%	-*
Breast disorder NOS	3.0%	1.2%
Abdominal pain	2.2%	1.2%
Cervical smear test positive	2.2%	-*
Leukorrhoea	1.6%	2.4%
Vaginitis	1.1%	2.4%

	Activelle (n=371)	Placebo (n=82)
<b>RESISTANCE MECHANISM DISORDERS</b>		
Infection NOS	2.2%	1.2%
Infection viral	3.8%	4.9%
Moniliasis genital	3.8%	-*
<b>RESPIRATORY SYSTEM DISORDERS</b>		
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%
<b>SECONDARY TERMS</b>		
Injury accidental	5.9%	2.4%
Other events	5.1%	2.4%
Cyst NOS	2.2%	1.2%
<b>SKIN AND APPENDAGES DISORDERS</b>		
Rash	2.2%	2.4%
Pruritus genital	1.6%	-*
Acne	1.3%	1.2%
Pruritus	1.1%	2.4%
<b>URINARY SYSTEM DISORDERS</b>		
Haematuria	1.1%	1.2%
Urinary tract infection	1.1%	2.4%

\*No adverse events reported

The most frequently reported adverse events in the clinical trials with Activelle® were breast pain / tenderness and headache reported in approximately 10-20% of patients.

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<sup>®</sup> study.

### **Less Common Clinical Trial Adverse Drug Reactions (<1%)**

**Gastrointestinal:** Abdominal distension.

**Immune system:** Hypersensitivity, see also *Skin and subcutaneous tissue disorders*.

**Metabolism and nutrition:** Fluid retention.

**Musculoskeletal, connective tissue and bone:** Leg cramps.

**Nervous system disorders:** Migraine.

**Skin and subcutaneous tissue:** Alopecia.

**Vascular disorders:** Thrombophlebitis superficial/deep; Pulmonary embolism.

### **Abnormal Hematologic and Clinical Chemistry Findings**

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

### **Post-Market Adverse Drug Reactions**

The following events have been spontaneously reported during five years experience (i.e. 1998 - 2002) with Activelle<sup>®</sup> in clinical practice representing a total of 2,301,955 woman - years and a reporting rate of < 1/10,000 patient years.

**Neoplasm benign and malignant:** Endometrial cancer

**Psychiatric disorders:** Insomnia, anxiety, libido decreased, libido increased

**Nervous system disorders:** Dizziness

**Eye disorders:** Visual disturbances

**Vascular disorders:** Hypertension aggravated

**Gastronintestinal disorders:** Dyspepsia, vomiting

**Hepatobiliary disorders:** Gallbladder disease, cholelithiasis, cholelithiasis aggravated, cholelithiasis re-occurrence

**Skin and subcutaneous disorders:** Seborrhea, rash, angioneurotic edema

**Reproductive system and breast disorders:**

Hyperplasia endometrial, vulvovaginal pruritus

**Investigations:** Weight decreased, blood pressure increased

## 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.

Estrogens may diminish the effectiveness of anticoagulant, antidiabetic and antihypertensive agents.

Preparations inducing liver enzymes (eg, barbiturates, hydantoin, carbamazepine, meprobamate, phenylbutazone or rifampin) may interfere with the activity of orally administered estrogens.

### Drug-Drug Interactions

**Table 2 – Established or Potential Drug-Drug Interactions**

Drug Class	Ref	Effect	Clinical comment
Anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepine), anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz)	C	Reduce plasma concentrations of estrogens	Therapeutic monitoring is recommended
	C	Increase plasma concentrations of estrogens	Therapeutic monitoring is recommended
Protease inhibitors (e.g. ritonavir, nelfinavir)	C	Increase plasma concentration of estrogens	Therapeutic monitoring is recommended
Imidazoles (e.g. ketoconazole)			

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

### Drug-Food Interactions

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

Administration of ActiVelle<sup>®</sup> with food did not modify the bioavailability of E<sub>2</sub>, although food increased AUC<sub>0-72</sub> for NET by 19% and decreased C<sub>max</sub> for NET by 36%.

Grapefruit juice may increase plasma concentrations of estrogen.

### **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.

### **Drug-Laboratory 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 norepinephrine-induced platelet aggregability; decreased antithrombin III;
- increased thyroxin-binding globulin (TBG), leading to increased circulating total thyroid hormone (T<sub>4</sub>) as measured by column or radioimmunoassay; free T<sub>3</sub> resin uptake is decreased, reflecting the elevated TBG; free T<sub>4</sub> 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.

### **Drug-Lifestyle Interactions**

None identified.

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

Activelle® is a continuous combined hormone replacement therapy 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 transferring from another continuous combined HRT product, treatment with Activelle® [may be started on any convenient day. In women transferring from sequential HRT regimens, treatment should start right after their withdrawal bleeding has ended.

### **Recommended Dose and Dosage Adjustment**

For the treatment of moderate to severe vasomotor symptoms, 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.

### **Missed Dose**

If the patient has forgotten to take a tablet, the tablet should be taken as soon as possible within the next twelve 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.

## **OVERDOSAGE**

For management of a suspected drug overdose, contact your regional Poison Control Centre.

### **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. Over dosage with estrogen may cause nausea, breast discomfort, fluid retention, bloating or vaginal bleeding in women. Progestin (e.g. norethindrone acetate) overdose has been characterized by depressed mood, tiredness, acne and hirsutism.

### **Treatment of overdose**

Overdose may be manifested by nausea and vomiting. Symptomatic treatment should be given.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

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

**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-hysterectomized women.

## **Pharmacodynamics**

### **Estrogen pharmacology**

Estradiol, E<sub>2</sub>, 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<sub>2</sub> 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<sub>2</sub> 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 progestogen 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 progestogen for an adequate time period reduces the incidence of endometrial hyperplasia and carcinoma in women with intact uteri who are receiving estrogen replacement therapy.

### **Pharmacokinetics**

<b>TABLE 3 - PHARMACOKINETIC PARAMETERS OF Activelle® after single dose</b>	
<b>Component / metabolite</b>	<b>1 mg E<sub>2</sub>/ 0.5 mg NETA Arithmetic Mean SD n=25</b>
<b>17β-estradiol (E<sub>2</sub>)<sup>1</sup></b>	
AUC (pg/ml*h)	706 ± 252
C <sub>max</sub> (pg/ml)	29.7 ± 9.4
t <sub>max</sub> (h)	6.8 ± 2.9
t <sub>1/2</sub> (h)	13.2 ± 4.7
<b>Estrone (E<sub>1</sub>)<sup>1</sup></b>	
AUC (pg/ml*h)	3741 ± 1446
C <sub>max</sub> (pg/ml)	230 ± 89
t <sub>max</sub> (h)	5.7 ± 1.4
t <sub>1/2</sub> (h)	12.2 ± 4.6
<b>Norethindrone (NET)</b>	
AUC (pg/ml*h)	23681 ± 9023 (n=24)
C <sub>max</sub> (pg/ml)	5308 ± 1510
t <sub>max</sub> (h)	1.0 ± 0.0
t <sub>1/2</sub> (h)	11.4 ± 2.7

<sup>1</sup>baseline adjusted

### **Absorption and Distribution:**

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. 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 and Excretion:**

Metabolism of E<sub>2</sub>, 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<sub>1</sub> and E<sub>2</sub> and between esterified and nonesterified forms. 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<sup>®</sup>, a peak plasma concentration is reached within 5-8 hours. The most important metabolites of norethindrone are isomers of 5 $\alpha$ -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<sup>®</sup> 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.

**Gender:** Activelle<sup>®</sup> is not indicated for use in male population.

**Race:** No specific information available.

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

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

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

### **STORAGE AND STABILITY**

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

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

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.

### **Non-medicinal ingredients**

Tablet core : lactose monohydrate, maize starch, copovidone, talc, magnesium stearate.

Film-coating : hypromellose, triacetin, talc.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance: 17 $\beta$ -estradiol

**Proper name:** Estradiol (hemihydrate) USP/Ph.Eur.

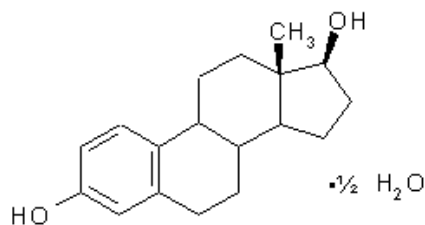
**Chemical name:**

1. 17 $\beta$ -estradiol  $\frac{1}{2}$  H<sub>2</sub>O
2. Estra-1, 3, 5 (10)-triene, 3, 17 $\beta$ -diol hemihydrate

**Molecular formula:** C<sub>18</sub>H<sub>24</sub>O<sub>2</sub>

**Molecular Mass:** 281.4

**Structural formula:**



#### Physicochemical properties:

**Description:** White or almost white crystalline powder

**Solubility:** Practically insoluble in water.  $5.0 \times 10^{-3}$  g/L

**Melting point:** 173 - 179°C

**pKa:** 10.71

**n-octanol/water partition coefficient:**  
log P<sub>OW</sub> = 3.30

**Drug Substance: Norethindrone acetate**

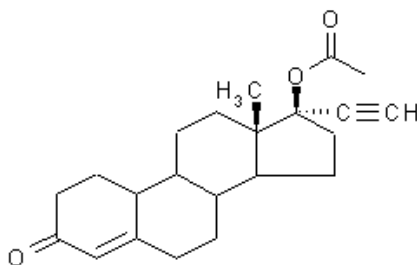
**Proper name:** Norethindrone acetate USP/Ph. Eur.

**Chemical name:** 1. 19-Norpregn-4-en-20-yn-3-one, 17- (acetyloxy)-, (17 $\alpha$ )  
2. 17-Hydroxy-19-nor-17 $\alpha$ -pregn-4-en-20-yn-3-one acetate

**Molecular formula:** C<sub>22</sub>H<sub>28</sub>O<sub>3</sub>

**Molecular Mass:** 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<sub>OW</sub> = 3.67.

## CLINICAL TRIALS

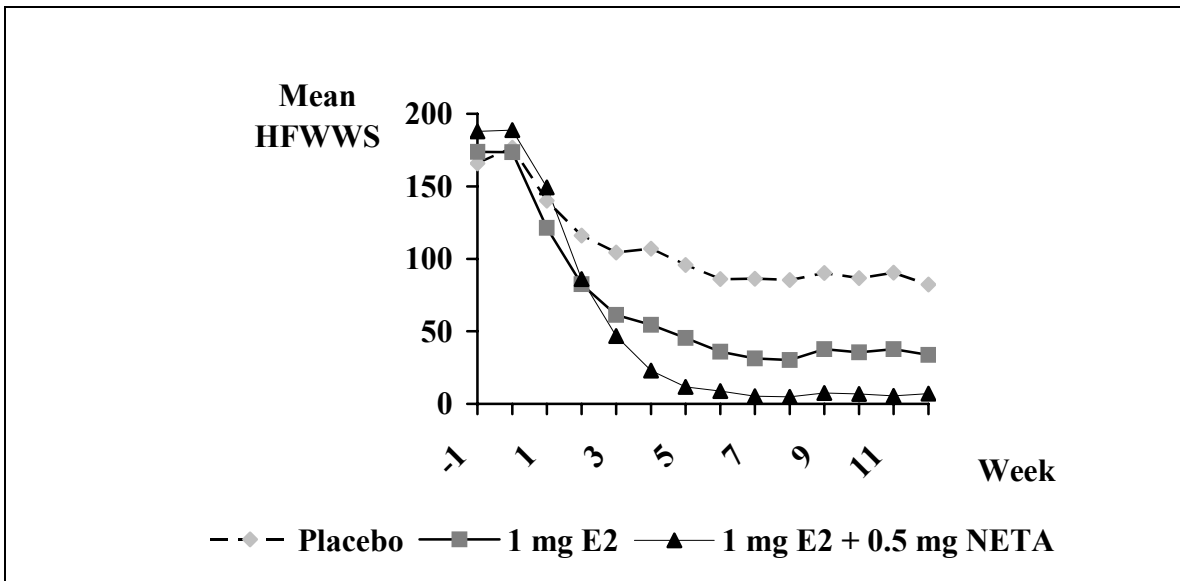
### Efficacy and Safety Studies

#### 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<sup>®</sup> in relief of moderate to severe vasomotor symptoms. The effects of both E<sub>2</sub> (N = 29) alone and Activelle<sup>®</sup> (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<sup>®</sup> compared to 1 mg E<sub>2</sub> 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<sub>2</sub>.

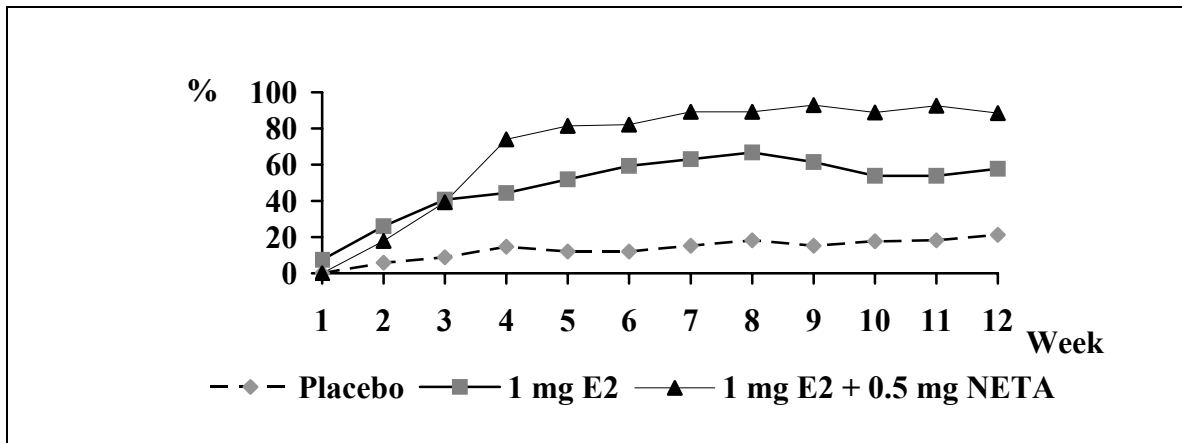
**Figure 1:**  
Effect of Activelle<sup>®</sup> on vasomotor symptoms as measured by a composite score of # and severity of hot flushes.



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<sub>2</sub>.

**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 E<sub>2</sub> and 1 mg E<sub>2</sub> + 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  $\geq$  3 months, who spontaneously complained of sweating and hot flushes. Subjects were randomized to one of the two arms of the trial 1mg E<sub>2</sub> + 0.25 mg NETA or 1 mg E<sub>2</sub> + 0.5 mg NETA. This trial compared climacteric symptoms of the two combination doses of E<sub>2</sub> and NETA respectively and with placebo.

## ***Study results: Effects on Menopausal Symptoms***

### ***Study results***

#### **Effects on Menopausal Symptoms**

The results of clinical studies indicate that the estrogen component of Activelle<sup>®</sup> 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<sub>2</sub> alone for symptom relief and it was concluded that both 1 and 2 mg of E<sub>2</sub> are effective while 1 mg of E<sub>2</sub> is the optimum dose.

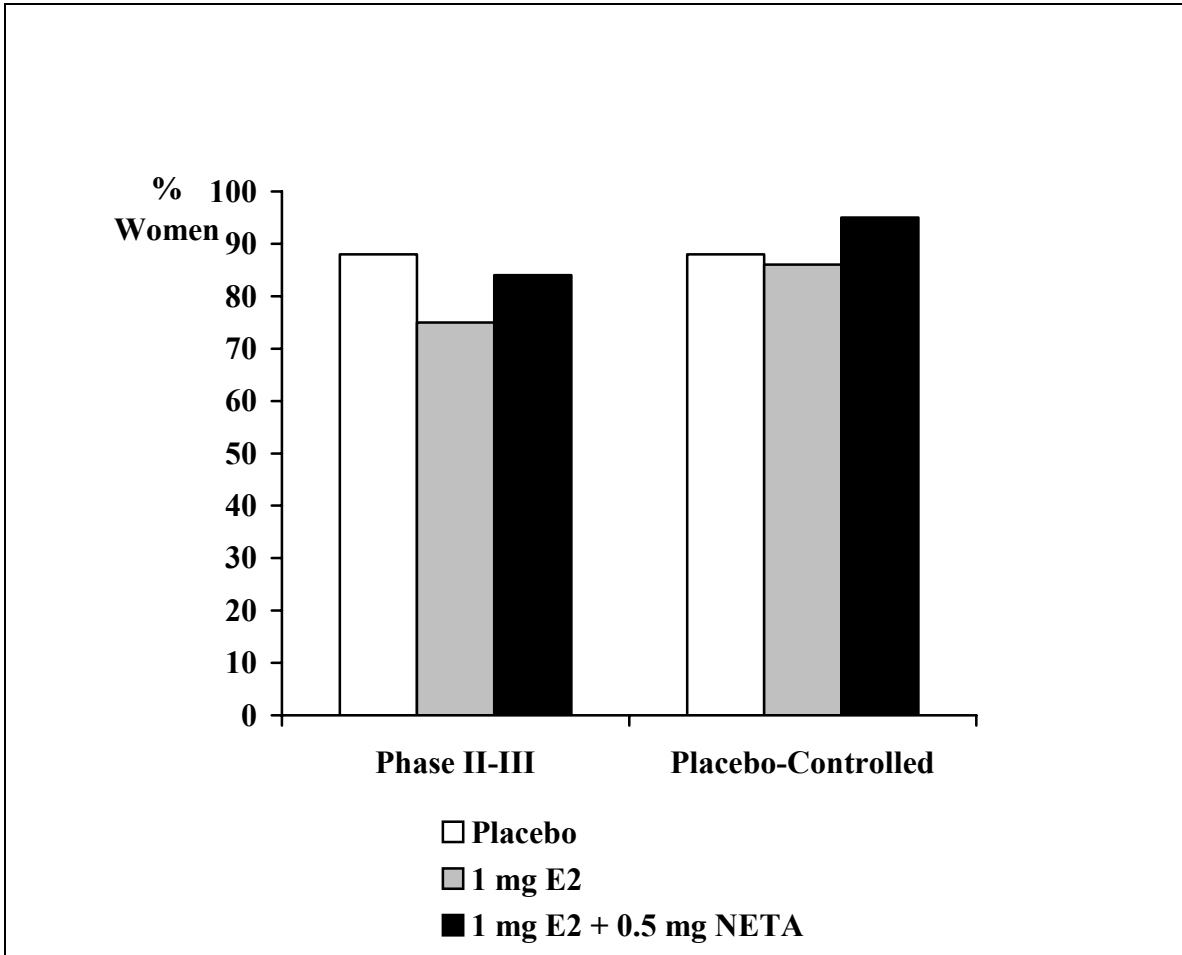
During the trial, KLIM/PD/1/N, a statistical decrease in the number of severe, moderate and mild hot flushes were reported in the active treatment groups. Efficacy in reducing vasomotor symptoms was demonstrated at 4 weeks of treatment, reaching and almost complete reduction in the score by week 8. Menopausal 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<sup>®</sup> than with 1 mg E<sub>2</sub> + 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 E<sub>2</sub> that will substantially reduce the incidence of endometrial hyperplasia when compared with 1 mg E<sub>2</sub> 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 E<sub>2</sub> with no norethindrone acetate or a combination of 1 mg of E<sub>2</sub> 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 progestogen component of Activelle<sup>®</sup>, norethindrone acetate (NETA), protects against the estrogen-induced proliferative changes in the endometrium. Long-term studies with Activelle<sup>®</sup> have documented that NETA when given concomitantly with E<sub>2</sub> 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<sub>2</sub> unopposed versus Activelle® treatment in clinical trials of postmenopausal women. The incidence of endometrial hyperplasia associated with unopposed E<sub>2</sub> (1 mg) was decreased significantly in patients treated with Activelle®.

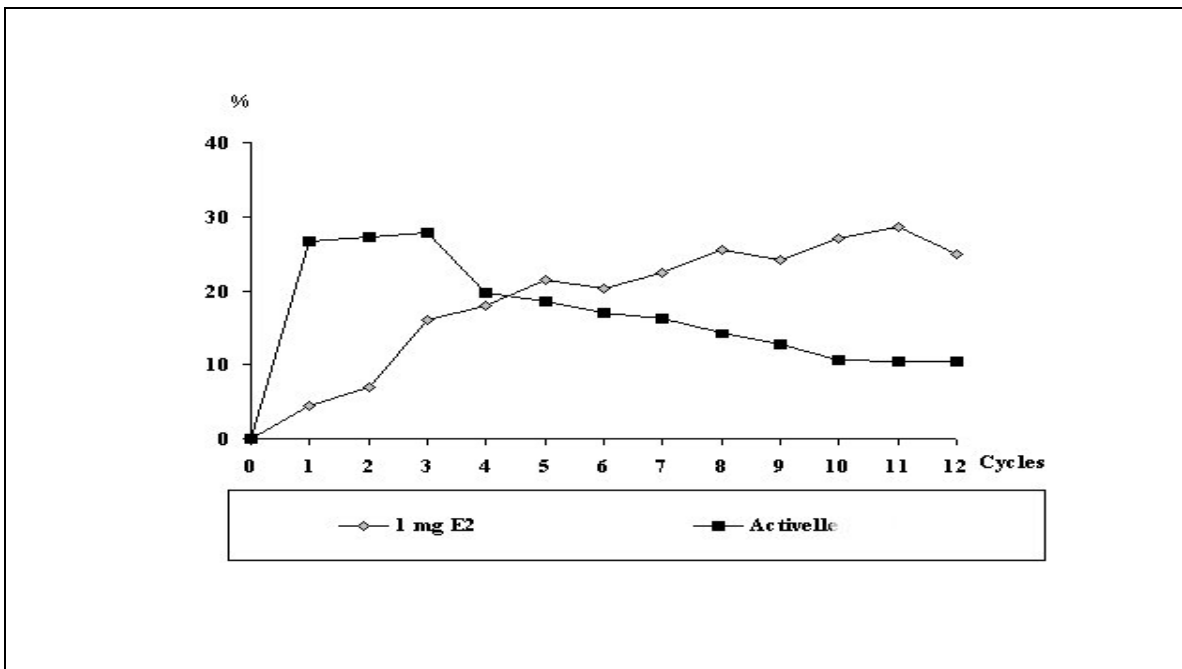
<b>TABLE 1 - INCIDENCE OF ENDOMETRIAL HYPERPLASIA IN A 12 MONTH STUDY</b>		
<b>Patients</b>	<b>Dose Groups</b>	
	<b>Activelle®</b>	<b>Unopposed 1 mg E<sub>2</sub></b>
	<b>1 mg E2/0.5 mg NETA</b>	
Total number of patients	295	296
# patients with histology evaluations	241	247
N (%) with hyperplasia	1 (0.4%)*	36 (14.6%)

\*simple hyperplasia without atypia

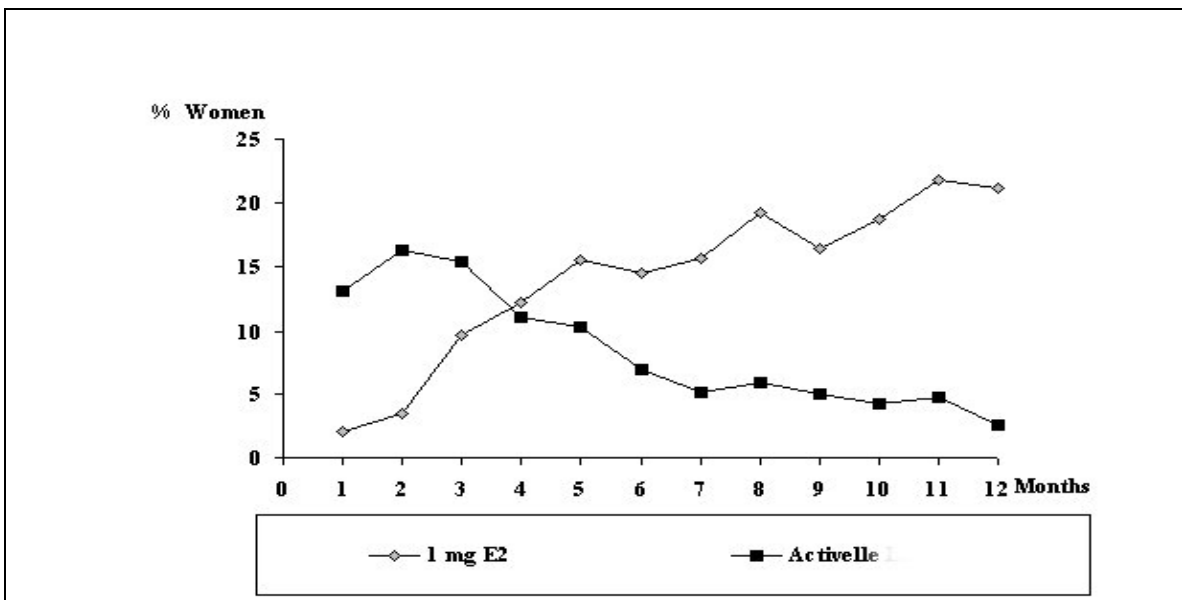
### **Effects on bleeding**

Use of a continuous combined Hormone Replacement Therapy 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.**



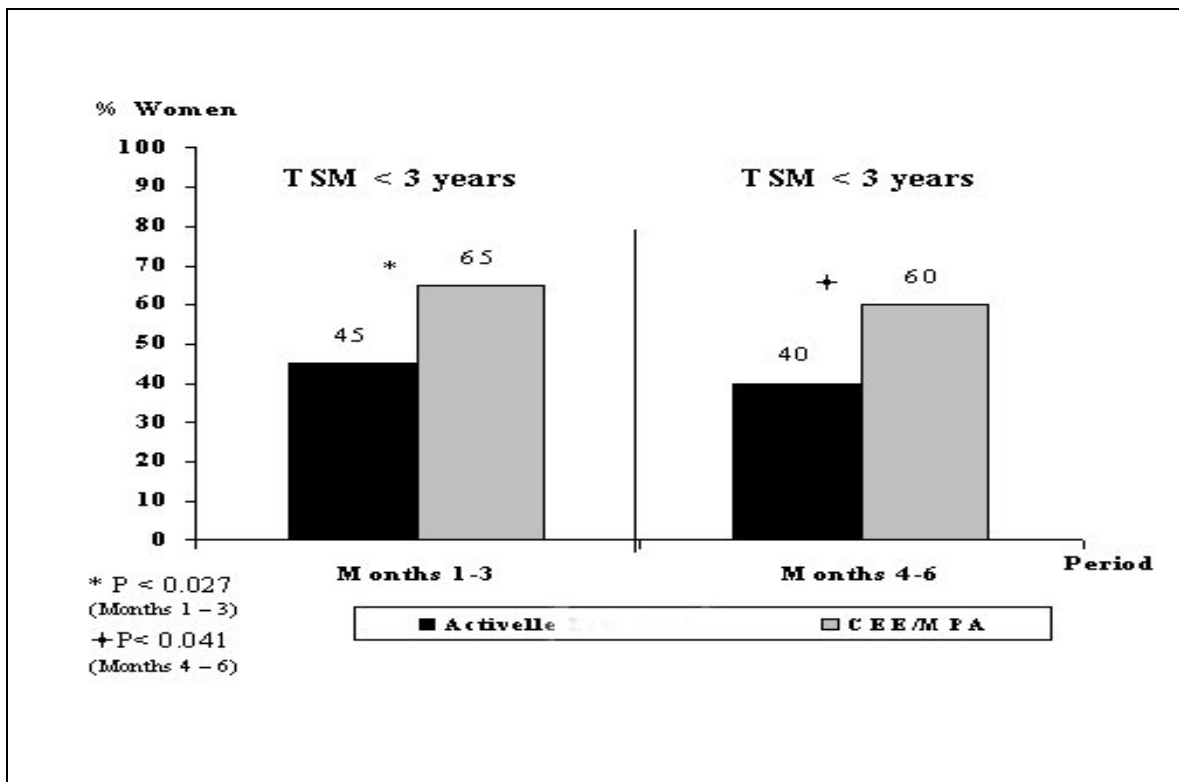
**Figure 5:**  
**Incidence of bleeding (without spotting)**



The incidence of bleeding with Activalle<sup>®</sup> 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 Activalle<sup>®</sup> 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 Activalle<sup>®</sup> was significantly lower during 6 months of therapy than with CEE 0.625 mg and MPA 2.5 mg.

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



TSM = Time Since Menopause

### Lipid Effects

The effect of Activalle<sup>®</sup> 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 2.

Activelle<sup>®</sup> significantly decreases total cholesterol and LDL-cholesterol compared to placebo. Activelle<sup>®</sup> 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<sup>®</sup>, 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<sup>®</sup>.

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

**Table 2 - Percent Change from Baseline in Lipid/Lipoprotein Parameters with Activelle<sup>®</sup> and Placebo**

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

\*significantly (p<0.05) different from baseline

## Hemostatic Changes

The effect of Activellev<sup>®</sup> in healthy postmenopausal women was evaluated in two placebo-controlled trials of 6 and 12 months duration.

Activellev<sup>®</sup> significantly decreases factor VII activity compared to placebo and unopposed estradiol. Combined E<sub>2</sub> and NETA appears to decrease factor VII activity. Fibrinogen is not modified during treatment with Activellev<sup>®</sup>; this is in contrast with the significant increase in fibrinogen observed with placebo.

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

A summary of the changes in hemostatic parameters assessed after 12 months of treatment with Activellev<sup>®</sup> is displayed in Table 3.

**Table 3 - Percent Change from Baseline in Activellev<sup>®</sup> Compared to Placebo**

Parameter	Activellev <sup>®</sup> n = 35	Placebo n = 34
Factor VII clotting activity	-23.1*	-4.0*
Fibrinogen	-3.7	12.4*
Antithrombin III activity	-9.8	-1.2
Plasminogen activator inhibitor-1 activity	-49.9*	2.6
Platelets	-0.9	-6.3

\* significantly (p<0.05) different from baseline

## Glucose Metabolism

The effect of Activellev<sup>®</sup> 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 Activellev<sup>®</sup>. There is no worsening of glucose tolerance with Activellev<sup>®</sup> 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<sup>®</sup> did not change compared to placebo. Finally, glycemic control measured by HBA<sub>1c</sub>, was found to improve with Activelle<sup>®</sup> compared to placebo.

## **DETAILED PHARMACOLOGY**

### **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 17 $\beta$ -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**

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.

## **MICROBIOLOGY**

Not applicable.

## **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.

## REFERENCES

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## PART III: CONSUMER INFORMATION

**Activelle®**

**1 mg Estradiol  
0.5 mg Norethindrone acetate**

**Film-coated tablets**

**This leaflet is part III of a three-part "Product Monograph" published when Activelle® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Activelle®. Contact your doctor or pharmacist if you have any questions about this drug.**

### ABOUT THIS MEDICATION

#### What the medication is used for:

Activelle® is approved for use in the following situations:

- ◆ To treat moderate to severe vasomotor symptoms (uncomfortable feelings of heat, flushing and sweating) that can occur as a result of the lower estrogen levels associated with menopause.
- ◆ To treat vulval and vaginal atrophy (changes in the vagina and/or external genitalia as a result of the low estrogen levels associated with menopause). Vulval and vaginal atrophy can contribute to symptoms such as itching, burning or dryness in or around the vagina, difficulty or burning during urination and pain while having sex.

Activelle® should only be used in women with an intact uterus.

Activelle® should be used only under the supervision of a doctor, with regular follow-up at least once a year to identify side effects associated with its use. Your first follow-up visit should be within 3 to 6 months of starting 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 doctor. Your doctor may recommend some blood tests.

You should carefully discuss the risks and benefits of hormone replacement therapy (HRT) with your doctor. You should regularly talk with your doctor about whether you still need treatment with HRT.

#### What it does:

The estrogen hormone is called estradiol (E2) and will help relieve your menopausal symptoms. Estradiol is identical to the estrogen produced naturally by your body. Activelle® replaces the estrogen in your body, which decreases naturally at menopause. Estrogen therapy can help reduce or eliminate these symptoms.

The progestin hormone is called norethindrone acetate (NETA) and will help to reduce the risk of endometrial hyperplasia (stimulation of growth of the lining of the uterus), which could lead to cancer of the lining of the uterus (womb).

#### When Activelle® should not be used:

- If you have known hypersensitivity to this drug or any of its ingredients or to the components of the container
- If you have liver dysfunction or disease as long as liver function tests have failed to return to normal
- If you have known or suspected estrogen-dependent or progestin-dependent malignant neoplasia (e.g. endometrial cancer)
- If you have endometrial hyperplasia
- If you have known, suspected, or past history of breast cancer
- If you have undiagnosed abnormal genital bleeding
- If you are or think you might be pregnant
- If you have an active or past history of arterial thromboembolic disease (e.g. stroke, myocardial infarction and/or coronary disease)
- If you have an active or past history of confirmed venous thromboembolism (such as deep vein thrombosis, pulmonary embolism) or active thrombophlebitis
- If you have partial or complete loss of vision due to ophthalmic vascular disease
- If you have porphyria
- If you have migraine
- If you are breastfeeding

#### What the medicinal ingredients are:

1 mg Estradiol  
0.5 mg Norethindrone acetate

#### What the important nonmedicinal ingredients are:

Hypromellose  
Lactose monohydrate  
Magnesium stearate  
Maize starch  
Talc  
Triacetin  
Copovidone

**What dosage forms it comes in:**

Activelle® is 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.

**WARNINGS AND PRECAUTIONS****Serious Warnings and Precautions**

The Women's Health Initiative (WHI) trial is a large clinical study that assessed the benefits and risks of oral combined *estrogen plus progestin* therapy and oral *estrogen-alone* therapy compared with placebo (a pill with no active ingredients) in postmenopausal women.

The WHI trial indicated an increased risk of myocardial infarction (heart attack), stroke, breast cancer, pulmonary emboli (blood clots in the lungs) and deep vein thrombosis (blood clots in the large veins) in postmenopausal women taking oral combined *estrogen plus progestin*.

Therefore, you should highly consider the following:

- There is an increased risk of developing invasive breast cancer, heart attack, stroke and blood clots in both lungs and large veins with the use of estrogen plus progestin therapy
- Estrogens with or without progestins should not be used for the prevention of heart disease or stroke.
- Estrogens with or without progestins should be used at **the lowest effective dose** and for the **shortest period of time** possible. Regular medical follow-up is advised.

**Breast Cancer**

The results of the WHI trial indicated an increased risk of breast cancer in post-menopausal women taking combined *estrogen plus progestin* compared to women taking placebo.

The results of the WHI trial indicated no difference in the risk of breast cancer in postmenopausal women with prior hysterectomy taking *estrogen-alone* compared to women taking placebo.

Estrogens with or without progestins should not be taken by women who have a personal history of breast cancer.

In addition, women with a family history of breast cancer or women with a history of breast lumps, breast biopsies or abnormal mammograms (breast x-rays) should consult with their doctor before starting HRT.

Women should have a mammogram before starting HRT and at

regular intervals during treatment as recommended by their doctor.

Regular breast examinations by a doctor and regular breast self-examinations are recommended for all women. You should review the technique for breast self-examination with your doctor.

**Overgrowth of the lining of the uterus and cancer of the uterus**

The use of *estrogen-alone* therapy by post menopausal women who still have a uterus increases the risk of developing endometrial hyperplasia (overgrowth of the lining of the uterus), which increases the risk of endometrial cancer (cancer of the lining of the uterus).

The purpose of adding a progestin medication to estrogen therapy is to reduce the risk of endometrial hyperplasia.

You should discuss progestin therapy and risk factors for endometrial hyperplasia and endometrial carcinoma with your doctor. You should also report any unexpected or unusual vaginal bleeding to your doctor.

If you have had your uterus removed, you are not at risk of developing endometrial hyperplasia or endometrial carcinoma. Progestin therapy is therefore not generally required in women who have had a hysterectomy.

**Ovarian cancer**

Prolonged use of hormone replacement therapy has been associated with an increased risk of ovarian cancer.

**Heart Disease and Stroke**

The results of the WHI trial indicated an increased risk of stroke and coronary heart disease in post-menopausal women taking combined *estrogen plus progestin* compared to women taking placebo.

The results of the WHI trial indicated an increased risk of stroke, but no difference in the risk of coronary heart disease in post-menopausal women with prior hysterectomy taking *estrogen-alone* compared to women taking placebo.

**Abnormal Blood Clotting**

The results of the WHI trial indicated an increased risk of blood clots in the lungs and large veins in post-menopausal women taking combined *estrogen plus progestin* compared to women taking placebo.

The results of the WHI trial indicated an increased risk of blood clots in the large veins, but no difference in the risk of blood clots in the lungs in post-menopausal women with prior hysterectomy taking *estrogen-alone* compared to women taking

placebo.

The risk of blood clots also increases with age, if you or a family member has had blood clots, if you smoke or if you are severely overweight. The risk of blood clots is also temporarily increased if you are immobilized for long periods of time and following major surgery. You should discuss risk factors for blood clots with your doctor since blood clots can be life-threatening or cause serious disability.

**Gallbladder Disease**

The use of estrogens by postmenopausal women has been associated with an increased risk of gallbladder disease requiring surgery.

**Dementia**

The Women’s Health Initiative Memory Study (WHIMS) was a sub-study of the WHI trial and indicated an increased risk of dementia (loss of memory and intellectual function) in postmenopausal women age 65 and over taking oral combined *estrogen plus progestin* compared to women taking placebo.

The WHIMS indicated no difference in the risk of dementia in post-menopausal women age 65 and over with prior hysterectomy taking oral *estrogen-alone* compared to women taking placebo.

**BEFORE you use Activelle® talk to your doctor or pharmacist 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 a history of uterine fibroids or endometriosis;
- have a history of liver disease, jaundice (yellowing of the eyes and/or skin) or itching related to estrogen use or during pregnancy;
- have a history of migraine headaches;
- have 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, asthma or epilepsy (seizures);
- have a history of bone disease (this includes certain metabolic conditions or cancers that can affect blood levels of calcium and phosphorus);
- have been diagnosed with diabetes;

- have been diagnosed with porphyria (a disease of blood pigment);
- have a history of high cholesterol or high triglycerides;
- are pregnant or may be pregnant;
- are breastfeeding;
- have had a hysterectomy (surgical removal of the uterus);
- smoke.

Other existing conditions you should discuss with your health professional include: lupus; very low calcium levels; thyroid problems; fluid retention; gallbladder disease; depression; upcoming surgery and prolonged bed rest.

You should inform other doctors that you are taking Activelle® as certain laboratory tests may change during treatment.

**INTERACTIONS WITH THIS MEDICATION**

Tell your doctor or pharmacist if you are taking any other medications, including prescription medications, over-the-counter medications, vitamins or herbal products.

**Drugs that may interact with Activelle® include:**

- § drugs used for the treatment of epilepsy (e.g. phenobarbital, phenytoin and carbamazepine)
- § drugs used for tuberculosis (e.g. rifampicin, rifabutin)
- § drugs used for the treatment of HIV infections (e.g. nevirapine, efavirenz, ritonavir and nelfinavir)
- § herbal preparations containing St John’s Wort (*Hypericum perforatum*)

Drugs containing ketoconazole (a fungicide) may increase the effect of Activelle®.

Grapefruit juice may increase the effect of Activelle®.

**PROPER USE OF THIS MEDICATION**

You may begin treatment with Activelle® on any day that is convenient. However, if you switch from a sequential Hormone Replacement Therapy product, treatment should start right after your regular bleeding cycle (period) has ended.

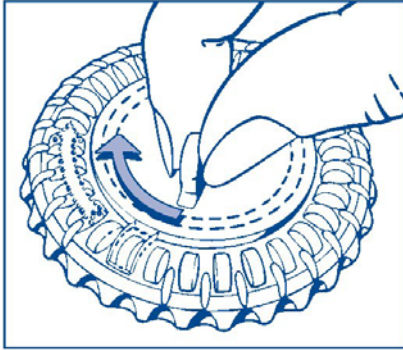
**Usual dose:**

Take 1 tablet once daily. Try to take Activelle® at the same time each day.

**How do I use the dial pack**

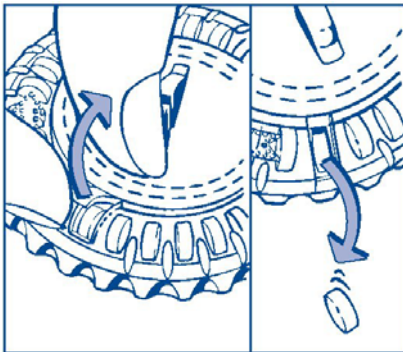
Activelle® is supplied in calendar dial packs of 28 white tablets. Follow these steps to use the calendar dial pack:

The first tablet to be taken is under the sealed opening in the see-through outer rim of the pack.



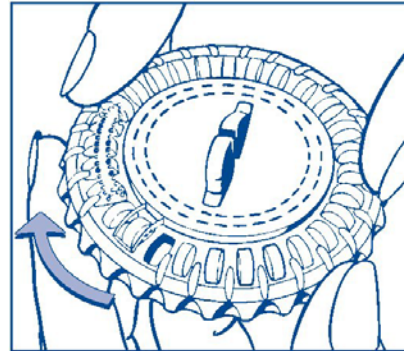
**1. Set the day reminder**

Turn the inner disc to set the day of the week opposite the little plastic tab.



**2. How to take the first tablet**

Break the plastic tab and tip out the first tablet.



**3. Every day**

Simply move the transparent dial clockwise one space as indicated by the arrow. Tip out the next tablet.

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

**Overdose:**

In general, excessive doses of estrogen and progestin may result in nausea, vomiting, abdominal cramps, headache, dizziness, and general ill feeling (malaise). If you take too much of the drug, contact your doctor or local Poison Control Centre.

**Missed Dose:**

If you miss a day, do not double your dose to make up for the missed tablet. Instead take the next tablet, at the regular time, the next day. Forgetting a dose may increase the likelihood of breakthrough bleeding and /or spotting.

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

The following side effects may occur during your treatment with Activelle®:

Very common

- § Vaginal bleeding
- § Breast pain / tenderness

Common

- § Genital infection with a fungus or vaginal inflammation
- § Headache
- § Nausea (feeling sick)
- § Abdominal (stomach) pain
- § Back or neck pain
- § Pain in arms or legs

**IMPORTANT: PLEASE READ**

§ Weight increase

Some women who have used HRT have reported the following side effects while taking estrogen and/or progestin:

- § Vomiting, abdominal discomfort (pressure pain, cramps), bloating
- § Breast swelling or tenderness or enlargement
- § Irregular bleeding or spotting
- § Change in the amount of cervical secretion
- § Involuntary muscle spasms
- § Hair loss or abnormal hairiness
- § Acne
- § Increase or decrease in weight.

If you think you are experiencing a side effect of the treatment, talk to your doctor.

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
	Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech or weakness or numbness in an arm or leg			✓
	Yellowing of the skin or eyes (jaundice)			✓

*This is not a complete list of side effects. For any unexpected effects while taking Activelle®, contact your doctor or pharmacist.*

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
<b>Common</b>	Abdominal pain, nausea or vomiting		✓	
	Pain in the leg			✓
	Unexpected vaginal bleeding		✓	
<b>Uncommon</b>	Breast lump		✓	
	Crushing chest pain or chest heaviness			✓
	Swelling of the leg			✓
	Persistent sad mood			✓
	Sharp pain in the chest, coughing blood or sudden shortness of breath			✓
	Sudden partial or complete loss of vision			✓

**HOW TO STORE IT**

Keep this and all drugs out of the reach of children.

Keep Activelle® at room temperature, (15° - 25°C) away from heat and humidity. Store in a dry place. Protect from light by keeping the dial-pack inside the outer carton.

Do not store any of your medications near the cooking area of the kitchen, the shower area of the bathroom or the glove compartment of your car as the temperature in these locations may go above normal room temperature from time to time. Do not store the calendar dial-pack in the refrigerator. Do not use Activelle® after the expiry date printed on the label of the calendar dial-pack and on the carton.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance by:

By toll-free telephone: 866-234-2345  
By toll -free fax: 866-678-6789  
Online: [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)  
By email: [CanadaVigilance@hc-sc.gc.ca](mailto:CanadaVigilance@hc-sc.gc.ca)

By regular mail:  
Canada Vigilance National Office  
Marketed Health Products Safety and Effectiveness  
Information Bureau  
Marketed Health Products Directorate  
Health Products and Food Branch  
Health Canada  
Tunney's Pasture, AL 0701C  
Ottawa ON K1A 0K9

*NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.*

**MORE INFORMATION**

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Novo Nordisk Canada Inc., at: 1-800-465-4334

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