PRODUCT MONOGRAPH

# Pr Activelle® *LD*

0.5 mg Estradiol and
0.1 mg Norethindrone acetate

Film-coated tablets

House Standard

Estrogenic Hormones/Progestin

Novo Nordisk Canada Inc.
300 – 2680 Skymark Avenue
Mississauga, Ontario
L4W 5L6

Date of Revision
June 21, 2016

Control No: 193505

# Table of Contents

# [Pr]Activelle® *LD*

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## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Clinically Relevant Nonmedicinal Ingredients |
|---|---|---|
| Oral | Film-coated tablet<br><br>0.5 mg estradiol (as estradiol hemihydrate) and 0.1 mg norethindrone acetate | Lactose monohydrate<br><br>*For a complete listing see* ***Dosage Forms, Composition and Packaging*** *section.* |

### INDICATIONS AND CLINICAL USE

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

- The treatment of moderate to severe vasomotor symptoms occurring in naturally or surgically induced estrogen deficiency states associated with menopause.

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

### CONTRAINDICATIONS

- Patients with known hypersensitivity to this drug or to any ingredient in the formulation or component of the container. For a 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, 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 due to ophthalmic vascular disease
- Porphyria
- Classical migraine
- Breastfeeding

## 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.[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 63.3 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.

### 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 **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 counselling.

***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 a 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 double-blind, randomised, multi-center study, 1,176 healthy postmenopausal women aged 44 years and older without evidence of endometrial abnormalities were given 12 months of treatment with continuous combined regimens of 1 mg E2 with 3 different doses of norethindrone acetate (NETA; 0.1 mg, 0.25 mg, 0.5 mg). All 3 doses, have shown similar incidences of endometrial hyperplasia at the end of 12 month study, and were significantly better at reducing the incidence of endometrial hyperplasia relative to E2 alone ($p<0.001$), based on 988 endometrial biopsies.

A second study assessed the endometrial thickness resulting from treatment with Activelle® *LD* (0.5 mg E2/0.1 mg NETA; n=185) versus a formulation containing 0.5 mg E2/0.25 mg NETA (n=173) or placebo (n=177). At 24 weeks, there were no differences between the groups in mean change of endometrial thickness, as evaluated by transvaginal ultrasound.

***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).[1]

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, 2,321 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.

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 **Drug-Laboratory Test Interactions**).

***Other Conditions***
Activelle® *LD* 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® *LD* tablets. 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 such as abdominal or orthopaedic surgery to lower limbs, or during periods of prolonged immobilization. Treatment should not be restarted until the woman is completely mobilised.

**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 woman 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® *LD*.

**Immune**

***Angioedema***
Estrogen may induce or exacerbate symptoms of angioedema, in particular in woman 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.

**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 re-evaluated.

***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 **Contraindications** and **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.

**Sexual Function/Reproduction**
See **Warnings and Precautions – Special Populations.**

**Special Populations**

**Pregnant Women:** Activelle® *LD* is contraindicated during pregnancy.

If pregnancy occurs during medication with Activelle® *LD* tablets, 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® *LD* should not be used when breastfeeding.

**Pediatrics**: Activelle® *LD* tablets are 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® *LD* 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 estrogen/progestin combination 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 drug 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® *LD* pivotal trial at a frequency of ≥1% are shown in Table 1 below. The regimens evaluated Activelle® *LD* over a 6-month treatment period

**Table 1: Treatment-Emergent Adverse Events with Possible or Probable Relationship Reported at a Frequency of ≥ 1% with Activelle® *LD***

| | **Activelle® *LD* (n=194)** | **Placebo (n=200)** |
|---|---|---|
| ***Gastrointestinal disorder*** | | |
| Nausea | 3% | 2% |
| Dyspepsia | 2% | -* |
| Abdominal distension | 1% | -* |
| Abdominal pain | 1% | 2% |
| Diarrhea | 1% | -* |
| ***Musculoskeletal and connective tissue*** | | |
| Back pain | 1% | -* |
| ***Nervous System*** | | |
| Headache | 11% | 8% |
| Dizziness | 1% | -* |
| **Vascular disorder** | | |
| Vaginal hemorrhage | 25% | 12% |
| Hot flush | 2% | 3% |
| ***Urogenital/Reproductive System*** | | |
| Endometrial thickening | 9% | 4% |
| Uterine leiomyoma | 3% | 2% |
| Ovarian cyst | 2% | -* |
| Vaginal discharge | 1% | -* |
| Breast pain | 1% | -* |
| Vulvovaginal mycotic infection | 1% | -* |
| Uterine polyp | 1% | -* |

* No adverse events reported

The most frequently reported adverse events in the clinical trials with Activelle® *LD* tablets were vaginal hemorrhage (any release of blood from uterus), endometrial thickening (double layer measured at ≥ 5 mm) and headache. The majority of AEs occurred with similar frequency in the treatment groups and were classified as mild or moderate in severity. As expected, the incidence of vaginal bleeding was higher in the continuous combined treatment groups Activelle® *LD* (25%) than in the placebo group (12%).

There were no reports of thromboembolic events in any treatment group. Clinically important symptoms related to the breast (breast discomfort, breast pain and tenderness) were reported by < 2% of subjects treated with the Activelle® *LD* regimens, which was comparable with the placebo group.

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

**Gastrointestinal:** Abdominal pain upper; constipation; epigastric discomfort; gastritis; stomach discomfort

**General and Administration Site Conditions:** Malaise; suprapubic pain

**Musculoskeletal, Connective Tissue and Bone:** Musculoskeletal stiffness; neck pain; pain in extremity

**Nervous System Disorders:** Migraine; disturbance in attention; mental impairment; restless legs syndrome; stress incontinence

**Reproductive System and Breast:** Breast tenderness; breast discomfort; vulvovaginal dryness; cervical cyst

**Skin and Subcutaneous Tissue Disorders:** Pruritus genital; acne; skin irritation

**Cardiac Disorders**: Chest discomfort; chest pain

**Vascular Disorders:** Hypertension; varicose vein

**Respiratory, Thoracic and Mediastinal Disorders:** Epistaxis

**Renal and Urinary Disorders:** Fluid retention; urinary retention

**Infections and Infestations:** Salpingitis; vaginal candidiasis

**Other:** Post procedural hemorrhage; liver function test abnormal

**Abnormal Hematologic and Clinical Chemistry Findings**

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

**Post-Market Adverse Drug Reactions**

The adverse events presented below have been reported by women taking Activelle® *LD* or a higher estradiol/norethindrone acetate formulation (Activelle® 1 mg/0.5 mg). They have been spontaneously reported and are, by an overall judgment, considered possibly related to treatment.

**Cardiac Disorders:** Myocardial infarction

**Eye Disorders:** Visual disturbances

**Gastronintestinal 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

If adverse symptoms persist, the prescription of HRT should be re-considered.

## 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.

### 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 |

### Drug-Food Interactions

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 made 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 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 thyroxine-binding globulin (TBG), leading to increased circulating total thyroid hormone (T4) as measured by column or radioimmunoassay; T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered;
- other binding proteins may be elevated in serum i.e., 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 2-4 weeks.

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

**Drug-Lifestyle Interactions**

None identified.

## DOSAGE AND ADMINISTRATION

**Dosing Considerations**

Activelle® *LD* is a low-dose continuous combined Hormone Replacement Therapy (HRT) product 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® *LD* 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.

**Recommended Dose and Dosage Adjustment**

One tablet of Activelle® *LD* (estradiol 0.5 mg and norethindrone acetate 0.1 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 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.

## 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**
Treatment should be symptomatic.

| For management of a suspected drug overdose, contact your regional Poison Control Centre. |
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## 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-hysterectomised women.

**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 follicule-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 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

**Table 3: Pharmacokinetic Parameters after Administration of 2 Tablets of Activelle® *LD* to Healthy Postmenopausal Women**

| | 2 x Activelle® LD (n=24) Mean[a] (%CV)[b] |
|---|---|
| Estradiol[c] ($E_2$) | |
| $AUC_{0-t}$ (pg/mL*h) | 697.3 (53) |
| $C_{max}$ (pg/mL) | 26.5 (37) |
| $t_{max}$ (h): median (range) | 6.5 (0.5-16.0) |
| $t_{1/2}$ (h)[d] | 14.5[e] (27) |
| Estrone[c] ($E_1$) | |
| $AUC_{0-t}$ (pg/mL*h) | 4469.1 (48) |
| $C_{max}$ (pg/mL) | 195.5 (37) |
| $t_{max}$ (h): median (range) | 6.0 (1.0 -9.0) |
| $t_{1/2}$ (h)[d] | 10.7 (44)[f] |
| Norethindrone (NET) | |
| $AUC_{0-t}$ (pg/mL*h) | 8407.2 (43) |
| $C_{max}$ (pg/mL) | 2375.4 (41) |
| $t_{max}$ (h): median (range) | 0.8 (0.7-1.3) |
| $t_{1/2}$ (h) | 11.4 (36)[g] |

AUC = area under the curve, 0 – last quantifiable sample
$C_{max}$ = maximum plasma concentration,
$t_{max}$ = time at maximum plasma concentration,
$t_{1/2}$ = half-life,
[a] geometric mean; [b] geometric % coefficient of variation; [c] baseline unadjusted data; [d] baseline adjusted data ; [e] n=16; [f] n=13; [g] n=21

**Absorption and Distribution:**
Following oral administration of Activelle® *LD* tablets, estradiol in micronized form, rapid absorption from the gastrointestinal tract occurs. The half-life of estradiol is about 15 hours. It circulates bound to sex hormone binding globulin (SHBG) (37%) and to albumin (61%), while only approximately 1-2% is unbound.

After oral administration of an Activelle® *LD* tablet, norethindrone acetate is rapidly absorbed and transformed to norethindrone (NET). The terminal half-life of NET is about 9-11 hours. NET binds to SHBG (36%) and to albumin (61%).

**Metabolism and Excretion:**
After rapid absorption from the gastrointestinal tract, estradiol undergoes a first-pass metabolism in the liver and other enteric organs, and reaches a peak plasma concentration of approximately 24 pg/mL (CV 38 %) (after administration of two Activelle® *LD* tablets) within 5-8 hours.

Metabolism of estradiol, occurs mainly in the liver and the gut but also in target organs, and involves the formation of less active or inactive metabolites, including estrone, catecholestrogens and several estrogen sulfates and glucuronides. Estrogens are excreted with the bile, hydrolysed and reabsorbed (enterohepatic circulation), and mainly eliminated in urine in biologically

inactive form.

After absorption, norethindrone undergoes first-pass metabolism in the liver and other enteric organs, and reaches a peak plasma concentration of approximately 2.4 ng/mL (CV 41 %) (after administration of two Activelle® *LD* tablets) within 0.5-1.5 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.

The pharmacokinetics of estradiol are not influenced by NET.

**Special Populations and Conditions**

**Pediatrics:** Activelle® *LD* tablets are not indicated for use in a pediatric population. 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® *LD* tablets are not indicated for use in a 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® *LD* tablets are white, round, biconvex, film-coated tablets engraved with NOVO 291 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 0.5 mg (as the hemihydrate) and norethindrone acetate 0.1 mg.

**Non-medicinal ingredients**

Tablet core: lactose monohydrate, maize starch, hydroxypropylcellulose, talc, magnesium stearate

Film-coating: hypromellose, triacetin, talc

# PART II: SCIENTIFIC INFORMATION

## PHARMACEUTICAL INFORMATION

**Drug Substance: Estradiol**

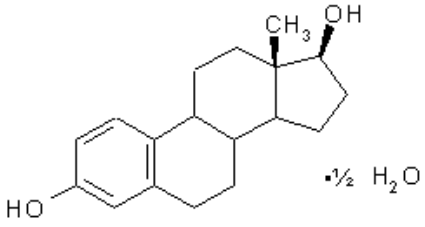
**Proper name:** Estradiol USP

**Chemical name:** 1. Estra-1, 3, 5 (10)-triene, 3, 17ß-diol

**Molecular formula:** $C_{18}H_{24}O_2$

**Molecular Mass:** 272.39

**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 $P_{OW}$ =3.30

**Drug Substance: Norethindrone acetate**

**Proper name:** Norethindrone acetate USP

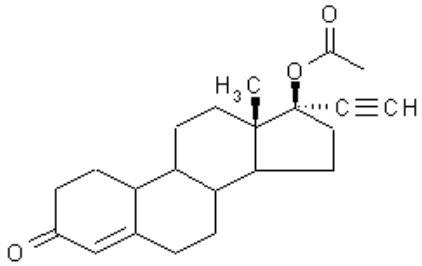
**Chemical name:** 1. 19-Norpregn-4-en-20-yn-3-one, 17- (acetyloxy)-, (17α)

2. 17-Hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one acetate

**Molecular formula:** $C_{22}H_{28}O_3$

**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 $P_{OW}$ = 3.67.

## CLINICAL TRIALS

Activelle® *LD* is a low-dose continuous combined hormone replacement therapy (HRT) for use in postmenopausal women. Activelle® *LD* was designed to use the minimum effective dose combination of estradiol (E2) and norethindrone acetate NETA for relief of vasomotor symptoms and endometrial protection. Activelle® *LD* contains 0.5 mg of estradiol (E2) and 0.1 mg norethindrone acetate (NETA).

### ***Efficacy and Safety Studies***

### Effects on Menopausal Symptoms

#### *Study demographics and trial design*

A pivotal study, ALD-1537**,** was designed to identify the optimal NETA dose (0.1 mg or 0.25 mg) to be used in combination with 0.5 mg E2. This was a six month double-blind, randomised, parallel-group, placebo-controlled trial that comprised a 2-3 week screening period to assess baseline menopausal symptoms, followed by 24 weeks of treatment. The trial population was postmenopausal women with an intact uterus, target age 46-65 years, with a minimum of seven moderate to severe hot flushes per day or 50 per week. A total of 575 healthy postmenopausal women were randomized to receive Activelle® *LD* or placebo: 194 to Activelle® *LD*, 182 to 0.5 mg E2 + 0.25 mg NETA, and 201 to placebo. The subjects' mean age was 55.5 years (range 44-65 years).

Supportive data for the choice of the E2 and NETA doses used in Activelle® *LD* were provided by clinical trials.

**Table 4: Study Population and Subject Disposition: Studies of Effects on Vasomotor Symptoms**

| Study | ALD-1537 |
|---|---|
| Number of subjects randomised | 577 |
| **Demographic details** | |
| Age (years) | |
| mean | 55.5 |
| (range) | (44-65) |
| Race | |
| White (%) | 95 |
| Black (%) | 0 |
| Asian/Pacific Islander (%) | 1 |
| Not available (%) | 4 |
| Other (%) | 0 |
| **Key criteria for inclusion** | |
| Months since spontaneous amenorrhoea | I: 12 or more months<br>II: 6 or more months<br>III unknown |
| FSH (mIU/mL) | I not specified<br>II & III >40 |
| E2 (pg/mL) | I not specified<br>II & III <25 |
| Intact uterus | Yes |
| Endometrial thickness (mm) | <5.0 |
| Minimum moderate to severe hot flushes | |
| per day | 7 |
| per week | 50 |
| **Disposition** | |
| Number (%) patients | |
| Treated | 575 (99%) |
| Completed study | 508 (88%) |
| Withdrawn | 67 (12%) |
| Reasons for withdrawal (n, %) | |
| Adverse event | 31 (5%) |
| Ineffective therapy | 21 (4%) |
| Protocol non-compliance | 8 (1%) |
| Other reason | 9 (2%) |

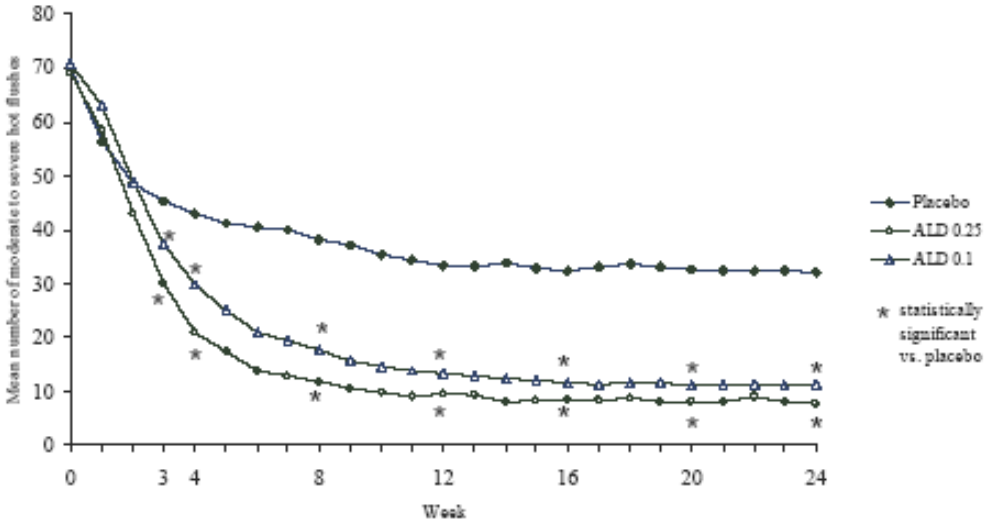
***Study results: Effects on Menopausal Symptoms***

***Study results***

In the pivotal study of Activelle® *LD*, the primary efficacy endpoint was the mean change in the number of moderate to severe hot flushes per week from baseline to week 8 and the mean change in severity score of moderate to severe hot flushes from baseline. The severity score was defined as SS1 = (2x number of moderate hot flushes + 3x number of severe hot flushes)/(number of moderate + number of severe hot flushes).

Compared to placebo, Activelle® *LD* treatments significantly reduced the number of moderate to severe hot flushes beginning at treatment week 3 (Figure 1). The change from baseline in the number of moderate to severe hot flushes per week in the Activelle® *LD* and formulation containing 0.5 mg E2 + 0.25 mg NETA groups were significantly different from placebo ($p \leq 0.001$) at weeks 3 through 24, however the two active groups were not significantly different from each other.

**Figure 1: Mean Number of Moderate to Severe Hot Flushes by Week (Study ALD-1537, ITT Population)**




*ALD 0.25 is not approved for use in Canada
** ALD 0.1 = Activelle® *LD*

Following Activelle® *LD* treatment, there was a decrease in the severity score of moderate to severe hot flushes with a mean change of -9.1 in the Activelle® *LD* group by week 8. In the placebo group a slight and more gradual decrease was seen, with a mean change of -3.4 by week 8.

The reduction in hot flush severity score was statistically significant when comparing Activelle® *LD* with placebo from week 3 to week 24 (p=0.001).

The treatment differences at week 4 were -1.3 (CI -2.1; -0.7) for Activelle® *LD* compared with placebo; at week 8 they were -5.1 (CI -7.1; -3.4) for Activelle® *LD* compared with placebo, and at week 12 they were -6.1 (CI -8.6; -4.2) for Activelle® *LD* compared with placebo.

A weekly weighted hot flush score which was a composite score incorporating the weekly number of hot flushes and the severity of each hot flush was also assessed. The weekly weighted hot flush score was calculated by multiplying the number of mild hot flushes by a factor of one, the number of moderate hot flushes by a factor of two, and the number of severe hot flushes by a factor of three, and then adding these scores on a weekly basis.

Following Activelle® *LD* treatment, there was a decline in the Hot Flush Weekly Weighted Score (HFWWS), from a mean score of 185.8 to 48.2 in the Activelle® *LD* group at week 8. In the placebo group, a slight and more gradual decrease in the HFWWS was seen, from a mean score of 183.5 at baseline to 101.1 at week 8. A statistically significant treatment difference ($p < 0.001$) was seen for all time points when comparing Activelle® *LD* with placebo.

Other efficacy endpoints assessed in this study were: responder analysis, Greene Climacteric Scale, urogenital symptom score.

Responders were defined as subjects with at least a 90% improvement in HFWWS from baseline. Analysis of the percentage of responders in the pivotal ALD study showed a statistically significant treatment effect at weeks 4, 8, 12 and 24 (all $p = 0.001$; Table 5).

**Table 5: Percentage of Responders (Pivotal ALD Study: ITT Population)**

| | **ALD 0.1** | | **Placebo** | |
|---|---|---|---|---|
| Week | % Responders | CI | % Responders | CI |
| 4 | 21* | 15, 27 | 10 | 5, 14 |
| 8 | 44* | 37, 51 | 13 | 8, 17 |
| 12 | 56* | 49, 63 | 20 | 14, 25 |
| 24 | 66* | 59, 73 | 23 | 17, 28 |

* statistically significant compared to placebo (p=0.001)

The Greene Climacteric Scale was assessed at Visits 2 to 6. The Greene Climacteric Scale comprises 21 symptoms in three groups (Psychological Factors, Somatic Factors, Vasomotor Factors) with a separate question regarding sexual interest. Greene Climacteric Scale mean total symptom scores decreased during the treatment period, with Activelle® *LD* mean values dropping from 18.0 at baseline to 8.0 at week 8. There was a smaller reduction in score in the placebo group, from 17.7 to 12.2. There was a statistically significant treatment difference ($p = 0.001$) for all time points when comparing Activelle® *LD* with placebo.

Most of the subjects in the pivotal ALD study experienced mild urogenital symptoms at baseline such that the mean urogenital symptom score was below 1 at week 0 in all treatment groups. Changes in the urogenital symptom score could not achieve statistical significance.

Laboratory investigations were carried out in a subset of 157 women from trial ALD-1537, for 24 weeks, to examine lipid, hemostasis parameters and glucose metabolism parameters. Routine

hematology and biochemistry evaluations were performed on blood samples taken during the course of trial ALD-1537, involving 575 women over 24 weeks.

No clinically significant results were observed.

## 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 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

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.

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**PART III: CONSUMER INFORMATION**

**[Pr]Activelle® *LD***

**0.5 mg Estradiol and**
**0.1 mg Norethindrone acetate**

**Film-coated tablets**

**This leaflet is Part III of a three-part "Product Monograph" published when Activelle® *LD* 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® *LD*. Contact your doctor or pharmacist if you have any questions about this drug.**

## ABOUT THIS MEDICATION

**What the medication is used for:**
During menopause, the amount of estrogen produced by a woman's body drops. This can cause symptoms such as hot face, neck and chest ('hot flushes'). Activelle® *LD* alleviates these symptoms after menopause. You will only be prescribed Activelle® *LD* if your symptoms seriously affect your daily life.

Activelle® *LD* is approved for use in the following situation:
- 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.

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

Activelle® *LD* 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 3-6 months of start of 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® *LD* replaces the estrogen in your body, which decreases naturally at menopause.

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® *LD* 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 disease and your liver function tests have not returned to normal
- If you have known, suspected, or past history of estrogen-dependent or progestin-dependent malignant neoplasia (e.g. endometrial cancer)
- If you have excessive thickening of the womb lining (endometrial hyperplasia)
- If you have known, suspected, or past history of breast cancer
- If you have any unexplained vaginal bleeding
- If you are or think you might be pregnant
- If you are breastfeeding
- If you have, or previously have had a disease caused by blood clots in the arteries, such as a heart attack, stroke or angina
- If you have, or have ever had a blood clot in a vein (thrombosis), such as in the legs (deep venous thrombosis) or the lungs (pulmonary embolism)
- If you have partial or complete loss of vision due to ophthalmic vascular disease
- If you have porphyria
- If you have a migraine

If any of the above conditions appear for the first time while taking Activelle®*LD,* stop taking it at once and consult your doctor immediately.

**What the medicinal ingredients are:**
Estradiol
Norethindrone acetate

**What the nonmedicinal ingredients are:**
Hydroxypropylcellulose, hypromellose, lactose monohydrate, magnesium stearate, maize starch, talc, triacetin

**What dosage forms it comes in:**
Activelle® *LD* is available in calendar dial-packs of 1x28 tablets.

Each tablet contains estradiol 0.5 mg and norethindrone acetate 0.1 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*.

The WHI trial indicated an increased risk of stroke and deep vein thrombosis in postmenopausal women with prior hysterectomy (surgical removal of the uterus) taking oral *estrogen-alone*.

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.
- There is an increased risk of stroke and blood clots in the large veins with the use of *estrogen-alone* 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 postmenopausal 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.

See your doctor if you notice any changes such as:

- dimpling of the skin
- changes in the nipple

- any lumps you can see or feel

Additionally, you are advised to join mammography screening programs when offered to you. For mammogram screening, it is important that you inform the nurse/healthcare professional who is actually taking the x-ray that you use HRT, as this medication may increase the density of your breasts which may affect the outcome of the mammogram. Where the density of the breast is increased, mammography may not detect all lumps.

***Overgrowth of the lining of the uterus and cancer of the uterus***
The use of *estrogen-alone* therapy by postmenopausal 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***
In some studies, the use of *estrogen-alone* and *estrogen plus progestin* therapies for 5 or more years 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 postmenopausal 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 postmenopausal 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 postmenopausal 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 postmenopausal 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 postmenopausal women age 65 and over with prior hysterectomy taking oral *estrogen-alone* compared to women taking placebo.

**BEFORE you use Activelle® *LD* 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 and/or a history of excessive growth of the womb lining (endometrial

hyperplasia)
- have a history of liver disease or liver tumours, jaundice (yellowing of the eyes and/or skin) or 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, asthma or epilepsy (seizures)
- have gallbladder disease
- have a history of bone disease (this includes certain metabolic conditions or cancers that can affect blood levels of calcium and phosphorus)
- have a condition where your thyroid gland fails to produce enough thyroid hormone (hypothyroidism) and you are treated with thyroid hormone replacement therapy
- have been told that you 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 been diagnosed with porphyria (a disease of blood pigment)
- have a history of high cholesterol or high triglycerides
- have very low calcium levels
- have been diagnosed with depression
- in case of prolonged bed rest
- are pregnant or may be pregnant
- are breastfeeding
- have had a hysterectomy (surgical removal of the uterus)
- have a disease affecting the eardrum and hearing (otosclerosis)
- have lactose intolerance
- smoke

If you are going to have surgery, tell the surgeon that you are taking Activelle® *LD*. You may need to stop taking Activelle® *LD* at least 4 to 6 weeks before the operation to reduce the risk of a blood clot. Ask your doctor when you can start taking Activelle® *LD* again.

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

Activelle® *LD* 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. Speak to your doctor for advice.

## 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® *LD* include:**
- drugs used for the treatment of epilepsy (e.g. phenobarbital, hydantoin, phenytoin and carbamazepine)
- drugs used for tuberculosis (e.g. rifampicin, rifabutin)
- drugs used for the treatment of HIV or hepatitis infections (e.g. nevirapine, efavirenz, ritonavir, telaprevir and nelfinavir)
- anticoagulant, antidiabetic and antihypertensive drugs
- barbiturates
- herbal preparations containing St John's Wort (*Hypericum perforatum*)
- Ketoconazole (a fungicide)

Grapefruit juice may increase the effect of Activelle® *LD*.

## PROPER USE OF THIS MEDICATION

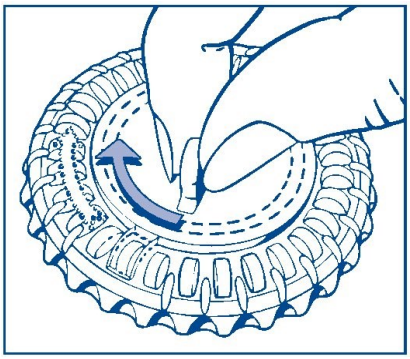
You may begin treatment with Activelle® *LD* on any day that is convenient. However, if you switch from a sequential Hormone Replacement Therapy product, treatment should start right after your regular bleeding cycle (period) has ended.

Your doctor should aim to prescribe the lowest dose to treat your symptoms for as short amount of time as necessary. Speak to your doctor if you think this dose is too strong or not strong enough.

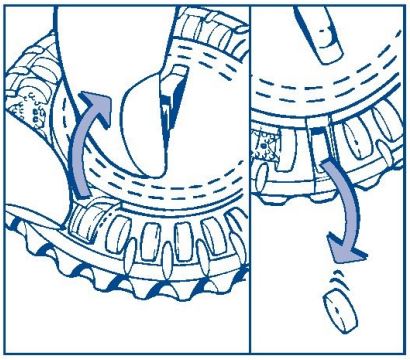
**Usual dose:**
Take 1 tablet once daily. Try to take Activelle® *LD* at the same time each day. Once you have finished all the 28 tablets in the pack, start a new pack continuing the treatment without interruption.

**How do I use the dial pack?**
Activelle® *LD* is supplied in calendar dial-packs of 28 white tablets. Follow these steps to use the calendar dial-pack:

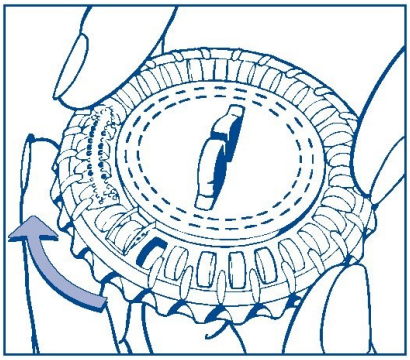
The first tablet to be taken is under the sealed opening in the see-through outer rim of the dial-pack.



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, breast discomfort, vomiting, bloating or vaginal bleeding, depressed mood, tiredness, acne or growth of body or facial hair.

If you think you have taken too much Activelle® *LD*, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

**Missed Dose:**
If you forget 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 the next dose should be taken at the normal time. Do not double your dose to make up for the missed tablet. Forgetting a dose may increase the likelihood of breakthrough bleeding and spotting.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

- Headache
- Irregular vaginal bleeding or spotting during the first 3-6 months of treatment. If bleeding continues or starts after the first 6 months, see your doctor as soon as possible.
- Change in the amount of cervical secretion
- Vaginal and genital itching
- Breast pain/tenderness, swelling or enlargement
- Hot flushes
- Bloating
- Uterine fibroid (benign tumour)
- Back or neck pain
- Involuntary muscle spasms
- Leg cramps
- Heartburn
- Increase or decrease in weight
- Hair loss or abnormal hairiness
- Acne
- Discolouration of the skin, especially of the face or neck, known as 'pregnancy patches' (chloasma)
- Red or purple discolourations of the skin and/or mucous membranes (vascular purpura)
- Painful reddish skin nodules (erythema nodosum)

**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 get immediate medical help |
|---|---|---|---|
| | Only if severe | In all cases | |
| **COMMON** | | | |
| Abdominal pain, nausea or vomiting | | ✓ | |
| **Edema:** Swelling of arms and legs | ✓ | | |
| **Depression:** Persistent sad mood | | | ✓ |
| Genital infection with a fungus or vaginal inflammation | ✓ | | |
| **Endometrial thickening** (enlarged lining of the womb), which can present itself as:<br>• Abnormal vaginal bleeding<br>• Vaginal discharge<br>• Abnormal cells visible in a cervical smear test | | ✓ | |

| 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 get immediate medical help** |
| | **Only if severe** | **In all cases** | |
| **UNCOMMON** | | | |
| **Allergic reaction:** Hives, itching, swelling, low blood pressure (paleness and coldness of skin, rapid heartbeat), sweating | | | ✓ |
| **Erythema multiforme**: Rash with target-shaped reddening or sores | | | ✓ |
| **Unexpected vaginal bleeding:**<br>• Lasting more than the first 6 months from the time you started taking Activelle® *LD and/or*<br>• Starting more than 6 months after you started taking Activelle® *LD and/or*<br>• Continuing after you have stopped taking Activelle® *LD* | | ✓ | |
| Breast lump | | ✓ | |
| **Heart attack:** Crushing chest pain or chest heaviness | | | ✓ |
| **Blood clot in the leg** (deep vein thrombosis): Leg swelling or pain | | | ✓ |
| **Blood clot in the lungs** (pulmonary embolism): Sharp pain in the chest, coughing blood, sudden shortness of breath, or difficulty in breathing | | | ✓ |
| **Blood clot in the eye:** Sudden partial or complete loss of vision | | | ✓ |
| **Stroke:** Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech or weakness or numbness in face, arm or leg | | | ✓ |
| **Jaundice:** Yellowing of the skin or eyes | | | ✓ |
| **Inflammation of a vein** (superficial thrombophlebitis): Pain, redness and bulging of vein | | | ✓ |
| Increase in blood pressure or worsening of high blood pressure | | ✓ | |
| Gallstones or gallbladder disease | ✓ | | |
| Migraine | | ✓ | |

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

**Reporting Side Effects**
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
**3 ways to report**:
- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Patient Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Patient Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

*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.*

## HOW TO STORE IT

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

Keep Activelle® *LD* 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® *LD* after the expiry date printed on the label of the calendar dial-pack and on the carton.

## MORE INFORMATION

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

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Last revised: June 21, 2016