PART III: CONSUMER INFORMATION

[Pr]Activelle®

1 mg Estradiol and
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:

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® alleviates these symptoms after menopause. You will only be prescribed Activelle® if your symptoms seriously affect your daily life.

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 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® 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® 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®, stop taking it at once and consult your doctor immediately.

What the medicinal ingredients are:
Estradiol
Norethindrone acetate

What the 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.

Each tablet contains estradiol 1 mg 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.*

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 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 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® 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®. You may need to stop taking Activelle® 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® again.

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

Activelle® is not a contraceptive. If it is less than 12 months since your last menstrual period or you are under 50 years old, you may still need to use additional contraception to prevent pregnancy. 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® 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®.

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 withdrawal bleeding 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.

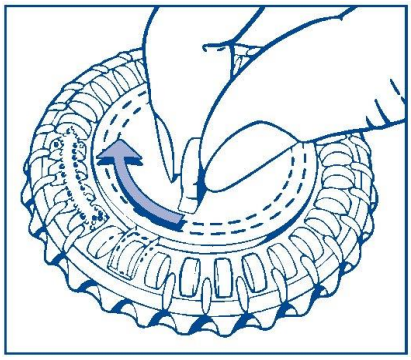
Usual dose:

Take 1 tablet once daily. Try to take Activelle® 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.

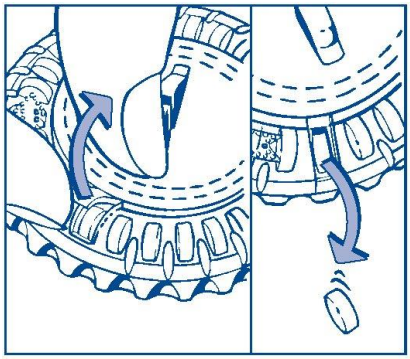
How do I use the dial pack?

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

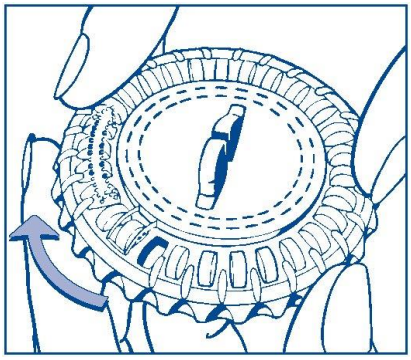
The first tablet to be taken is under the sealed opening in the see-through outer rim of the calendar dial-pack.



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®, 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®:

- 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	✓		

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**	
Endometrial thickening (enlarged lining of the womb), which can present itself as: • Abnormal vaginal bleeding • Vaginal discharge • Abnormal cells visible in a cervical smear test		✓	
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: • Lasting more than the first 6 months from the time you started taking Activelle® *and/or* • Starting more than 6 months after you started taking Activelle® *and/or* • Continuing after you have stopped taking Activelle®		✓	
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			✓

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**	
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®*, 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® 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.

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

IMPORTANT: PLEASE READ

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