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MENOPAUSE

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Disclosure

I have received speaker honorariums from the following companies:

- Merck Canada
- Pfizer Canada
- Bayer Inc.
- Novartis Pharmaceuticals Canada Inc.
- Triton Pharma Inc.

Diagnosis Menopause

- Menopause is defined as the final menstrual period
- Spontaneous menopause is recognized retrospectively after 12 months of amenorrhea and occurs at an average age of 51
- In women hysterectomy without BSO or presenting with a menstrual history that is inadequate to ascertain menopausal status
- Make presumptive diagnosis of menopause based on presence of VMS and repeated measures of FSH (at least 4-6 weeks apart).

Table 1. Definitions of Spectrum of Menopause

Menopause
Clinical status after the final menstrual period, diagnosed retrospectively after cessation of menses for 12 mo in a previously cycling woman and reflecting complete or nearly complete permanent cessation of ovarian function and fertility.

Spontaneous menopause
Cessation of menses that occurs at an average age of 51 y in the absence of surgery or medication (316–318).

Menopausal transition (or perimenopause)
An interval preceding the menopause characterized by variations in menstrual cycle length and bleeding pattern, mood shifts, vasomotor, and vaginal symptoms and with rising FSH levels and falling anti-Mullerian hormone and inhibin B levels, which starts during the late reproductive stage and progresses during the menopause transition (15, 319).

Climacteric
The phase in the aging of women marking the transition from the reproductive phase to the nonreproductive state. This phase incorporates the perimenopause by extending for a longer variable period before and after the perimenopause.

Climacteric syndrome
When the climacteric is associated with symptomatology.

Menopause after hysterectomy without oophorectomy
Spontaneous cessation of ovarian function without the clinical signal of cessation of menses.

Induced menopause
Cessation of ovarian function induced by chemotherapy, radiotherapy, or bilateral oophorectomy.

Early menopause
Cessation of ovarian function occurring between ages 40 and 45 in the absence of other etiologies for secondary amenorrhea (pregnancy, hyperprolactinemia, and thyroid disorders)

POI
Loss of ovarian function before the age of 40 y with waxing and waning course and potential resumption of menses, conception, and pregnancy (320). The prevalence of POI is approximately 1% (321) and is differentiated into idiopathic, autoimmune (associated with polyglandular autoimmune syndromes), metabolic disorders, and genetic abnormalities(including fragile X premutation).

Signs and Symptoms of Menopause

A. Vasomotor Symptoms

- 75% of postmenopausal ♀ in USA
- Associated diminished sleep quality
- Irritability
- Difficulty concentrating
- Reduced quality of life
- Poorer health status
- Can persist up to 7.4 years (study of Women's Health Across the Nation) and appear to be linked to cardiovascular (CV), bone and cognitive risks

B. Complaints related to the urogenital tract

C. Sleep Problems

D. Cognitive dysfunction and most disorders

E. Others → muscle and joint pains, headaches

Table 2. Conditions That May Cause or Mimic Vasomotor Events and That Can Be Distinguished From Menopausal Symptoms by History, Examination, and Investigations, as Indicated

Hormone excess
- Thyroid hormone excess
- Carcinoid syndrome (flushing without sweating)
- Pheochromocytoma (hypertension, flushing, and profuse sweating)

Dietary factors
- Alcohol
- Spicy food
- Food additives (eg, monosodium glutamate, sulfites)

Pharmaceuticals
- Chronic opioid use
- Opiate withdrawal
- SSRIs (may cause sweats)
- Nicotinic acid (intense warmth, itching lasting up to 30 min)
- Calcium channel blockers
- Medications that block estrogen action or biosynthesis

Chronic infection (increased body temperature)

Other medical conditions
- Postgastric surgery dumping syndrome
- Mastocytosis and mast cell disorders (usually with gastrointestinal symptoms)

Some cancers: medullary carcinoma of the thyroid,
- pancreatic islet-cell tumors, renal cell carcinoma, lymphoma

Anxiety disorders

Genitourinary Syndrome of Menopause

- Refers to the physical changes of the vulva, vagina and lower urinary tract that result from estrogen deficiency

- Common and Progressive condition that adversely affects health, sexuality and quality of lie of many menopausal women

Table 3. Genitourinary Syndrome of Menopause

Symptoms
- Vulvar pain, burning, or itching
- Vaginal dryness
- Vaginal discharge
- Dyspareunia
- Spotting or bleeding after intercourse
- Dysuria, urinary frequency, urgency
- Recurrent urinary tract infections

Signs, external genitalia
- Decreased labial size
- Loss of vulvar fat pads
- Vulvar fissures
- Receded or phimotic clitoris
- Prominent urethra with mucosal eversion or prolapse

Signs, vagina
- Introital narrowing
- Loss of elasticity with constriction
- Thin vaginal epithelial lining
- Loss of mature squamous epithelium
- Pale or erythematous appearance
- Petechiae, ulcerations, or tears
- Alkaline pH (5.5)
- Infection (yellow or greenish discharge

Assessment and Risk Management of Menopausal Women

1. Lifestyle
   - Smoking
   - Alcohol consumption
   - Exercise
   - Nutrition

2. Medical History
    - Cardiovascular disease
    - Hypertension
    - Diabetes mellitus
    - Venous thromboembolic disease
    - Breast disease
    - Cancer
    - Osteoporosis
    - Thyroid dysfunction
    - Auto Immune disorders
    - Migraines
    - Mental health problems
    - Current medication

3. Gynaecological History

4. Obstetrical History
   - Pre-eclampsia
   - Gestational Hypertension
   - Gestational Diabetes
   - Placental Abruption

5. Family History
   - Dyslipidemia
   - Osteoporosis
   - Diabetes mellitus
   - Cardiovascular Disease
   - VTE
   - Cancer
   - Dementia

Recommendations for Health Care Providers

1. A waist circumference ≥ 88 cm (35 in) for women is associated with an increased risk of health problems such as diabetes, heart disease, and hypertension and should be part of the initial assessment to identify risk (II-2A)

2 Tobacco-use status should be updated for all patients on a regular basis, (I-A) health care providers should clearly advise patients to quit, (I-C) the willingness of patients to begin treatment to achieve abstinence (quitting) should be assessed, (I-C) and every tobacco user who expresses the willingness to begin treatment to quit should be offered assistance (I-A)

3 Blood pressure should be assessed and controlled as women go through menopause (II-2B) If the systolic blood pressure is ≥ 140 mmHg and/or the diastolic blood pressure is ≥ 90 mmHg, a specific visit should be scheduled for the assessment of hypertension (III-A)

4. Women ≥ 50 years of age or postmenopausal and those with additional risk factors, such as current cigarette smoking, diabetes, and arterial hypertension, should have lipid-profile screening done. (II-2A)

5 A cardiovascular risk assessment using the Framingham Risk Score should be completed every 3 to 5 years for women aged 50 to 75 (II-2A)

6 A history of past pregnancy complications (preeclampsia, gestational hypertension, gestational diabetes, placental abruption, idiopathic preterm delivery, and/or fetal growth restriction) should be elicited since it can often predict an increased risk for premature cardiovascular disease and cardiovascular death and may inform decisions about the need for screening (II-2B)

Safety Considerations
Contraindications for Hormone Therapy

- Unexplained vaginal bleeding
- Severe active liver disease
- Prior estrogen-sensitive breast or endometrial cancer
- Coronary heart disease (CHD)
- Stroke
- Dementia
- Personal history or inherited high risk thromboembolic disease
- Porphyria cutanea tarda
- Hypertriglyceridemia
- Migraine with aura/caution

Major findings from the 2017 Hormone Therapy Position Statement of the North American Menopause Society

- Hormone therapy remains the most effective treatment for vasomotor symptoms (VMS) and the genitourinary syndrome of menopause and has been shown to prevent bone loss and fracture

The risks of hormone therapy differ depending on the type, dose, duration of use, route of administration, timing of initiation and whether a progestogen is added.

Treatment should be individualized to identify the most appropriate HT type, dose, formulation, route of administration and duration of use, using the best available evidence to maximize benefits and minimize risks with periodic re-evaluation of the benefits and risk of continuing or discontinuing HT.

For women aged younger that 60 years or who are within 10 years of menopause onset and have no contraindications, the benefit-risk ratio is most favorable for treatment of bothersome VMS and for those at elevated risk for bone loss or fracture

For women who initiate HT more than 10 or 20 years from menopause onset or are aged 60 years or older, the benefit-risk ratio appears less favorable because of the greater absolute risks of coronary heart disease, stroke, venous thromoboembolism and dementia.

Longer durations of therapy should be for documented indications such as persistent VMS or bone loss, with shared decision making and periodic re-evaluation.

For bothersome GSM symptoms not relieved with over-the-counter therapies and without indications for use of systemic HT, low dose vaginal estrogen therapy or other therapies are indicated.

Benefits of menopause hormone therapy

A. Vasomotor Symptoms

Estrogen therapy is the most effective treatment for VMS and improving QOL in symptomatic women.

B. Genitourinary Syndrome of Menopause

Estrogen therapy is the most effective treatment for GSM.

C. Sleep Disturbances

Hormone therapy improves sleep in women with bothersome nighttime VMS by reducing nighttime awakenings.

D. Anxiety and Depressive Symptoms

In small RCT's, estrogen therapy was effective in improving clinical depression in peri-menopausal but not post-menopausal women. Progestins may contribute to mood disturbance.

E. Dementia

Hormone therapy cannot be recommended at any age to prevent or treat a decline in cognitive function or dementia.

Estrogen therapy may have positive cognitive benefits when initiated immediately after early surgical menopause, but HT in the early natural post-menopause period has neutral effects on current cognitive function.

F. Arthralgia

Joint pain or stiffness and general aches or pains were improved in women receiving EPT.

Potential preventive benefits of menopausal hormone therapy

1. Bone Loss & Fracture

   RCT's, observational studies and meta-analyses consistently report reduction in bone loss with ET.

2. Type 2 Diabetes
   - RCTs and large observational studies reported that hormone therapy reduced the prevalence of self-reported diabetes by 14 to 19%.

- Hormone therapy may help attenuate abdominal adipose accumulation and the weight gains often associated with menopause transition

3. Colorectal Cancer
   In clinical trials, EPT was associated with a nonsignificant lower incidence of colorectal cancer in women ages 50-59.

4. Mortality

   Meta-analyses of RCTs report a significant reduction in all cause mortality in women who initiate HT when aged younger than 60 years and/or who are within 10 years from menopause onset.

* No protective effect if initiation > 10 years menopause onset

5. Cardiovascular Disease

   In women<60 years old, who are recently menopausal and with no evidence of cardiovascular disease, the initiation of estrogen-alone therapy reduces CHD and all cause mortality.

* It is not recommended to initiate hormone therapy beyond age 60 for primary prevention of CHD.

Risks of Menopause Hormone Therapy

A. Endometrial Cancer

Unopposed systemic ET in post-menopausal women with an intact uterus increases risk of endometrial cancer – Dose and Duration related

Adequate concomitant progestogen is recommended for women with a uterus.

B. Breast Cancer

Effect of HT on breast cancer risk depends on type HT, dose, duration of use, regimen, route of administration, prior exposure and individual characteristics.

- Possible increased risk of breast cancer associated with HT is small and estimated at less than 0.1% per annum (an incidence <1.0 per 1000 per year of use).

- Similar or lower than increased risks associated with common lifestyle factors such as reduced physical activity, obesity and alcohol consumption.

C. Stroke

- Menopause hormone may carry a small increased risk of stroke
- Suggestion that transdermal preparations have less impact on the risk of stroke than oral preparations.

D. VTE

- Risk VTE increases with age and presence of congenital or acquired thrombophilic disorders
- Careful assessment of personal and family Hx of VTE
- Risks of VTE events increases with oral hormone therapy but absolute risk is rare below age 60 years
- Observational studies point to a lower risk with low-dose transdermal therapy associated with progesterone.

E. Gallbladder and Liver

- Risk of gallstones, cholecystitis and cholecystectomy is increased with oral estrogen-alone and combination HT.

- Observational studies report lower risk with transdermal HT than with oral and with oral estradiol compared with CEE, but neither confirmed with RCT.

F. Ovarian Cancer

The association between HT use and ovarian cancer remains unclear

G. Lung Cancer

- There appears to be an overall neutral effect of HT on lung cancer incidence
- Smoking cessation should be encouraged

Non-Hormonal Therapies for Menopausal Symptoms

A. SSRI + SNRI
   - Paroxetine
   - Citalopram
   - Escitalopram
   - Venlafaxine
   - Desvenlafaxine

- Found to be effective for the treatment of hot flushes in several studies
- In 2013, FDA approved Paroxetine 7.5 mg daily to treat moderate to severe hot flushes associated with menopause
- Paroxetine should NOT be used in patient on Tamoxifen (Blocks conversions of Tamoxifen to active metabolites through CYP2D6)

B. Gabapentin

- Anti-epileptic drug
- 4 RCT confirmed moderate efficacy in relieving hot flashes
- Effects as a sedative and a reducer of vasomotor instability
- Works well bedtime as a sedation – side effects dissipate by morning
- Dose range 300-1200 mg (start 100 mg one hour prior bedtime and increase by 100 mg q 3 nights until relief of hot flashes, side affects or a maximum 900 mg

C. Pregabalin

D. Clonidine

- Centrally active alpha-2 adrenergic agonist – modestly more effective than placebo
- Side effects – dry mouth, dizziness, constipation, sedation
- Transdermal patches preferred over tablets because of more stable blood levels

E. OTC and alternative non-hormonal therapies for VMS

- Lack of inconsistent evidence for benefit for Botanicals, Black Cohosh, Omega-3 fatty acids, red clover, Vitamin E
- Mind/body alternatives including anxiety control, acupuncture, paced breathing, hypnosis

Treatment of Genitourinary Syndrome of Menopause

- Vaginal moisturizers when used regularly may provide an effective non-hormonal approach to alleviating symptoms.

- Vaginal lubricants - used to enhance sexual experience by alleviating vaginal dryness and preventing dyspareunia

Vaginal moisturizers and lubricants

Product (manufacturer)	Ingredients	Notes
Moisturizers		
Replens®	Water, carbomer, polycarbophil, paraffin, hydrogenated palm oil, glyceride, sorbic acid, and sodium hydroxide	Should be used 3 times weekly
Me Again™	Water, carbomer, aloe, citric acid, chlorhexidine deglutinate, sodium benzoate, potassium sorbate, diazolidinyl urea, and sorbic acid	
Vagisil® Feminine Moisturizer	Water, glycerin, propylene glycol, poloxamer 407, methylparaben, polyquaternium-32, propylparaben, chamomile, and aloe	
Feminease®	Water, mineral oil, glycerin, yerba santa, cetyl alcohol, and methyl paraben	Yerba santa (Eriodictyon spp), a plant native to the Pacific Northwest, is used as a moisturizer in place of aloe
K-Y® SILK-E®	Water, propylene glycol, sorbitol, polysorbate 60, hydroxyethylcellulose, benzoic acid, methylparaben, tocopherol, and aloe	
Lubricants		
Water-based		
Slippery Stuff®	Water, polyoxyethylene, methylparaben, propylene glycol, isopropynol	
Astroglide®	Water, glycerin, methylparaben, propylparaben, polypropylene glycol, polyquaternium, hydroxyethylcellulose, and sodium benzoate	Also sold in a glycerin-free and paraben-free formulation
K-Y® Jelly	Water, glycerin, hydroxyethylcellulose, parabens, and chlorhexidine	
Pre-Seed®	Water, hydroxyethylcellulose, arabinogalactan, paraben, and Pluronic copolymers	Promoted to women and their partners who are trying to conceive
Silicone-based		
ID® Millennium	Cyclomethicone, dimethicone, and dimethiconol	Less drying than other lubricants
Pjur® Eros	Cyclopentasiloxane, dimethicone, and dimethiconol	Compatible with a condom
Pink™	Dimethicone, vitamin E, aloe vera, dimethiconol, and cyclomethicone	Compatible with a condom
Oil-based		
Elégance Women's Lubricant	Natural oils	Does not contain alcohol, glycerin, or parabens; is **not** compatible with a condom

Adapted with permission from: Marshall DD, Iglesia C. A guide to lotions and potions for treating vaginal atrophy. OBG Management 2009; 21:29. Copyright © 2009 Dowden Health Media.

For women without a history of hormone (estrogen) dependent cancers who are seeking relief from symptoms of GSM that persist despite using vaginal lubricants and moisturizers – Recommend low dose, vaginal estrogen therapy:

- Low dose vaginal tablet
- Low dose vaginal creams
- Low dose vaginal ring

* Routine progestin co-therapy is not required for endometrial protection in women receiving vaginal estrogen therapy in an appropriate dose

Clinical Guidelines

1. Hormone therapy is the most effective treatment for VMS and GSM and has been shown to prevent bone loss and fracture

2. Benefits are most likely to out-weigh risks for symptomatic women who initiate HT when aged younger than 6 years or who are within 10 years of menopause onset

3. Hormone therapy should be individualized

4. Should use appropriate HT type, dose, formulation, route of administration and duration of use to meet treatment objective with periodic re-assessment of changes in a woman's health and anticipated benefits, risks and treatment goals

5. Assessment of risk for estrogen-sensitive cancers, bone loss, health disease, stroke and VTE is appropriate when counseling menopausal women

6. Decision making about HT should be incorporated into a broader discussion of lifestyle modification to manage symptoms and risk for chronic disease

Unsupported Hormone Therapies

Custom-Compounded Bioidentical Hormone Therapy

SOGC DOES NOT support the use of custom-compounded bioidenticals.

Custom-compounded bioidenticals hormone therapy **ARE NOT** regulated by Health Canada.

Examples of custom-compounded bioidenticals:

- Bi-est cream
- Tri-est cream
- Estriol cream
- Progesterone cream
- DHEA (dehydroepiandrosterone) tablets

SOGC DOES support the North American Menopause Society statement on Bioidentical Hormone Therapy:

"Concern arises with the bioidentical hormone medications that are "custom-compounded" (custom-mixed) recipes prepared by a pharmacist following an individual prescriber's order for a specific treatment. These medications do not have [HEALTH CANADA] approval because individually mixed recipes have not been tested to prove that the active ingredients are absorbed appropriately or provide predictable levels in blood and tissue. Further, there is no scientific evidence about the effects of these compounded medications on the body—both good and bad."

The Medical Letter Position (May 2010):

"There is no acceptable evidence that 'bioidentical' (custom-compounded) hormones are safe or effective. Patients should be discouraged from taking them."

Estrogens, oral*

Product / Manufacturer	Type of Estrogen	Dosage / Strength and Administration	Clinical Indication(s)
ESTRACE Shire Canada Inc.	17β-Estradiol	Tablet 0.5 mg 1 mg 2 mg (Daily)	• Symptomatic relief of menopausal symptoms • Adjunct to other therapeutics for the prevention of osteoporosis
PREMARIN Pfizer Canada Inc.	Conjugated equine estrogens	Tablet 0.3 mg 0.625 mg 1.25 mg (Daily)	• Relief of menopausal and postmenopausal symptoms • Prevention of osteoporosis • Atrophic vaginitis • Vulvar atrophy • Hypoestrogenism due to hypogonadism
C.E.S. Valeant Canada Ltd.	Conjugated estrogens	Tablet 0.3 mg 0.625 mg 0.9 mg 1.25 mg (Daily)	• Relief of menopausal and postmenopausal symptoms • Prevention and treatment of osteoporosis • Atrophic vaginitis • Hypoestrogenism due to hypogonadism

* No progestogen required in hysterectomized women.

Progestogens, oral

Product / Manufacturer	Type of Progestogen	Dosage / Strength and Administration	Clinical Indication(s)
PROMETRIUM Merck Canada Inc.	Micronized progesterone	Tablet 100 mg (Daily)	For women with intact uteri: adjunct to postmenopausal estrogen replacement therapy to significantly reduce the risk of endometrial hyperplasia and carcinoma
PROVERA Pfizer Canada Inc.	Medroxypro-gesterone acetate	Tablet 2.5 mg 5 mg 10 mg (Daily)	For women with intact uteri: adjunct to postmenopausal estrogen replacement therapy to significantly reduce the risk of endometrial hyperplasia and carcinoma

Combined estrogens and progestogens, transdermal***

Product / Manufacturer	Type of Estrogen and Progestogen	Dosage / Strength and Administration	Clinical Indication(s)
CLIMARA PRO Bayer Inc.	17β-Estradiol Levornogestrel (LNG)	Matrix patch 45 µg Estradiol + 15 µg LNG (Once weekly)	• Relief of menopausal and postmenopausal symptoms
ESTALIS Novartis Pharmaceuticals Canada Inc.	17β-Estradiol Norethindrone acetate (NETA)	Patch 50 µg Estradiol + 140 µg NETA 50 µg Estradiol + 250 µg NETA (Twice weekly)	• Relief of menopausal and postmenopausal symptoms • Atrophic vaginitis • Vulvar atrophy

*** Recommended only in patients with an intact uterus since the regimen includes a progestogen whose role is to prevent endometrial hyperplasia.

Combined estrogens and progestogens, oral

Product / Manufacturer	Type of Estrogen and Progestogen	Dosage / Strength and Administration	Clinical Indication(s)
ACTIVELLE Novo Nordisk Canada Inc.	Estradiol (as hemihydrate) Norethindrone acetate (NETA)	**Tablet** 1 mg Estradiol + 0.5 mg NETA (Daily)	• Relief of menopausal and postmenopausal symptoms • Vulvar or vaginal atrophy
ACTIVELLE *LD* Novo Nordisk Canada Inc.	Estradiol (as hemihydrate) Norethindrone acetate (NETA)	**Tablet** 0.5 mg Estradiol + 0.1 mg NETA (Daily)	• Relief of menopausal and postmenopausal symptoms
ANGELIQ Bayer Inc.	17β-Estradiol Drospirenone (DRSP)	**Tablet** 1 mg Estradiol + 1 mg DRSP (Daily)	• Relief of menopausal and postmenopausal symptoms • Atrophic vaginitis • Vulvar atrophy
femHRT Warner Chilcott Canada Co.	Ethinyl estradiol (EE) Norethindrone acetate (NETA)	**Tablet** 5 µg EE + 1 mg NETA (Daily)	• Relief of menopausal and postmenopausal symptoms • Atrophic vaginitis • Vulvar atrophy • Prevention of osteoporosis

Estrogens, transdermal*

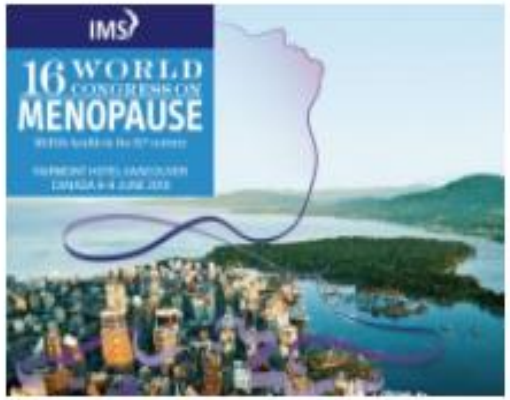
Product / Manufacturer	Type of Estrogen	Dosage / Strength and Administration	Clinical Indication(s)
CLIMARA Bayer Inc.	17β-Estradiol	**Patch** 0.025 mg 0.05 mg 0.075 mg 0.1 mg (Once weekly)	• Relief of menopausal and postmenopausal symptoms • Prevention of osteoporosis (Climara 25 is not indicated for the prevention of osteoporosis)
ESTRADERM Novartis Pharmaceuticals Canada Inc.	17β-Estradiol	**Patch** 0.025 mg 0.1 mg (Twice weekly)	• Relief of menopausal and postmenopausal symptoms • Prevention of osteoporosis
ESTRADOT Novartis Pharmaceuticals Canada Inc.	17β-Estradiol	**Patch** 0.025 mg 0.0375 mg 0.05 mg 0.075 mg 0.1 mg (Twice weekly)	• Relief of menopausal and postmenopausal symptoms • Prevention of osteoporosis

Estrogens, vaginal**

Product / Manufacturer	Type of Estrogen	Dosage / Strength and Administration	Clinical Indication(s)
ESTRAGYN VAGINAL CREAM Triton Pharma Inc.	Estrone	**Cream** 1mg/g 2-4g/applicator Supplied in tube of 45 g (Daily)	• Atrophic vaginitis • Kraurosis vulvae • Prurit vulvae
ESTRING Paladin Labs Inc.	17β-Estradiol	**Silastic ring** 2.0 mg (Continuous use for 3 months)	• Postmenopausal urogenital complaints due to estrogen deficiency such as: - Atrophic vaginitis - Dyspareunia - Dysuria - Urinary urgency
PREMARIN Pfizer Canada Inc.	Conjugated estrogens	**Cream** 0.625 mg/g 0.5-2 g/applicator Supplied in tubes of 14 g (Daily)	• Atrophic vaginitis • Dyspareunia • Kraurosis vulvae
VAGIFEM‡ Novo Nordisk Canada Inc.	17β-Estradiol	**Tablet** 0.025 mg *Initial dose:* 1 tablet daily for two weeks *Maintenance dose:* 1 tablet twice weekly with 3-4 dav interval	• Symptoms of atrophic vaginitis due to estrogen deficiency
VAGIFEM 10 Novo Nordisk Canada Inc.	17β -Estradiol	**Tablet** 0.01 mg *Initial dose:* 1 tablet daily for two weeks *Maintenance dose:* 1 tablet twice weekly	• Symptoms of vaginal atrophy due to estrogen deficiency

**Addition of a progestogen is not required.
‡ Will no longer be supplied by the manufacturer after December 30, 2011.

16th World Congress on Menopause



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