

## NOTICE

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The final version of this Health Canada guidance document **Product Monographs of Non-Contraceptive Estrogen/Progestin-Containing Products** is now available. Comments and suggestions received from the consultation on the draft version of the guidance were reviewed and considered in the finalization of this document.

This document is intended to replace the draft guidance document: *Product Monographs of Non-Contraceptive Estrogen/Progestin-Containing Products*.

Health Canada has initiated a Hormone Replacement Therapy (HRT) class labeling project in light of new safety information derived from the results of the Women's Health Initiative (WHI) trial and the Women's Health Initiative Memory Study (WHIMS).

In light of this new safety information that should be conveyed to health practitioners and their patients, Health Canada has developed the Guidance for Industry: *Product Monographs of Non-Contraceptive Estrogen/Progestin-Containing Products*. This document is intended to help the pharmaceutical industry revise the content of the Product Monograph and associated labeling materials.

The approach for implementing this guidance is as follows: All sponsors of non-contraceptive estrogen/progestin-containing products will be contacted by Health Canada and requested to update their labelling in accordance with this guidance. All sponsors will be required to comply with this guidance. Depending on the market status of the Canadian Reference Product (CRP), sponsors of generic products may be permitted to update the labelling their respective products immediately upon the finalization of the labelling for the CRP.

This and other Guidance documents are available on the website.

Should you have any questions regarding the content of the guidance, please contact

Bureau of Metabolism, Oncology and Reproductive Sciences,  
Therapeutic Products Directorate,  
Health Canada,  
Finance Building, A.L. 0202D2,  
Tunney's Pasture  
Ottawa, Ontario  
K1A 1B9

E-mail: [bmors\\_enquiries@hc-sc.gc.ca](mailto:bmors_enquiries@hc-sc.gc.ca)  
Telephone: (613) 941-3171  
Fax: (613) 941-1365



# **GUIDANCE FOR INDUSTRY**

## Product Monographs of Non-Contraceptive Estrogen / Progestin-Containing Products

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**Health Products and Food Branch**

<p>Our mission is to help the people of Canada maintain and improve their health.</p> <p style="text-align: right;"><i>Health Canada</i></p>	<p>HPFB's Mandate is to take an integrated approach to the management of the risks and benefits to health related to health products and food by:</p> <ul style="list-style-type: none"> <li>• Minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and,</li> <li>• Promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health.</li> </ul> <p style="text-align: right;"><i>Health Products and Food Branch</i></p>
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 Brooke Claxton Building, A.L. #0913A  
 Tunney's Pasture  
 Ottawa, Ontario  
 K1A 0K9

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 Fax: (613) 941-5366

*Également disponible en français sous le titre:* Monographies des produits non contraceptifs contenant des œstrogènes et des progestatifs

## FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with the policies and governing statutes and regulations. They also serve to provide review and compliance guidance to staff, thereby ensuring that mandates are implemented in a fair, consistent and effective manner.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document **may be** acceptable provided they are supported by adequate scientific justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this guidance, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidances.

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## 1 INTRODUCTION

### 1.1 Purpose

Health Canada initiated a Hormone Replacement Therapy (HRT) class labelling project in light of new safety information derived from the results of the Women's Health Initiative (WHI) trial<sup>1,2,3</sup> and the Women's Health Initiative Memory Study (WHIMS).<sup>6,7</sup>

In light of this new safety information that should be conveyed to health practitioners and their patients, the Therapeutic Products Directorate (TPD) has developed a document entitled *Guidance for Industry: Product Monographs of Non-Contraceptive Estrogen/Progestin-Containing Products*. This document is intended to help the pharmaceutical industry revise the content of the Product Monograph and associated labelling materials. TPD will continue to monitor the labelling of HRT products on an ongoing basis.

### 1.2 Inquiries

The Director's Office of the Bureau of Metabolism, Oncology and Reproductive Sciences can assist sponsors with questions concerning the preparation and filing of a draft product monograph or if further clarification is required (email: BMORS\_enquiries@hc-sc.gc.ca.)

### 1.3 Background

#### ***Description and Findings of the Women's Health Initiative (WHI) trial and the Women's Health Initiative Memory Study (WHIMS)***

The Women's Health Initiative (WHI) trial examined the health benefits and risks of combined *estrogen plus progestin* therapy and *estrogen-alone* therapy in postmenopausal women aged 50 to 79 years.<sup>1-3</sup> The *estrogen plus progestin* arm of the WHI trial indicated an increased risk of myocardial infarction (MI), stroke, invasive breast cancer, pulmonary emboli and deep vein thrombosis in postmenopausal women receiving treatment with combined conjugated equine estrogens (CEE, 0.625 mg/day) and medroxyprogesterone acetate (MPA, 2.5 mg/day) for 5.2 years compared to those receiving placebo.<sup>1</sup> The *estrogen-alone* arm of the WHI trial indicated an increased risk of stroke and deep vein thrombosis in hysterectomized women treated with CEE-alone (0.625 mg/day) for 6.8 years compared to those receiving placebo.<sup>2</sup>

The Women's Health Initiative Memory Study (WHIMS), a clinical substudy of the WHI, was designed to assess whether postmenopausal hormone replacement therapy (*estrogen plus progestin* or *estrogen-alone*) reduces the risk of dementia in women aged 65 and over and free of dementia at baseline.<sup>6,7</sup> Available data indicate that the use of combined *estrogen plus progestin* in women aged 65 and over may increase the risk of developing probable dementia<sup>6</sup>. The results of the *estrogen-alone* arm of the WHIMS did not indicate a statistically significant difference in the rate of probable dementia in women treated with estrogen-alone *versus* placebo<sup>7</sup>.

### ***The Hormone Replacement Therapy (HRT) Class Labelling Initiative***

TPD determined that safety information from the WHI trial should be conveyed to health care professionals and patients in the labelling for all HRT products. Based on the results of the *estrogen plus progestin* arm of the WHI trial, TPD developed an HRT Working Paper, entitled "Working Paper for Product Monographs of Non-Contraceptive Estrogen + Progestin Products" (February 2003), to assist the pharmaceutical industry to update the content of Product Monographs and associated labelling information for HRT products. Beginning in April 2003, labelling updates were requested from sponsors of combination estrogen plus progestin, estrogen-only, progestin-only and combination estrogen plus testosterone products indicated for use in menopausal women.

Subsequent to the development of the February 2003 HRT Working Paper, the results of the *estrogen-only* arm of the WHI trial and results of the WHIMS were published. The HRT Working Paper was therefore updated to incorporate additional results from the WHI and WHIMS and was renamed "Guidance for Industry: Product Monographs of Non-Contraceptive Estrogen/Progestin-Containing Products". This HRT guidance document also incorporates the new Product Monograph format effective October 1, 2004 as per *Guidance for Industry: Product Monograph*.

#### **1.4 Using the Guidance Document**

The *Guidance for Industry: Product Monographs of Non-Contraceptive Estrogen/ Progestin-Containing Products* is divided into sections that reflect the structure and format of a Product Monograph. This guidance provides specific instructions for each section of the Product Monograph that needs to be updated in accordance with the HRT Class Labelling Initiative. Additionally, references are made throughout this guidance to the related *Guidance for Industry: Product Monograph*, which came into effect on October 1, 2004.

#### **1.5 Scope and Application**

This guidance document applies to all human, prescription, non-contraceptive, estrogen/progestin-containing drug products indicated for use in menopause (commonly called "hormone replacement therapy" or "HRT".) Where appropriate, distinction is made between estrogen-only, progestin-only and combination estrogen-progestin HRT products.



## 2 PRODUCT MONOGRAPH STYLE GUIDE

The product monograph consists of three distinct parts:

- Part I: Health Professional Information**  
Contains information required for the safe and appropriate prescribing, dispensing and administering of the medication
- Part II: Scientific Information**  
Contains more in-depth and complete scientific/research information.
- Part III: Consumer Information**  
Contains information derived from Parts I and II written in lay language that helps the consumer understand what the medication is, how to use it, and what the potential side effects are.

For detailed Product Monograph style guidance, including instructions for formatting of headings and subheadings, please see Section 2 of the *Guidance for Industry: Product Monograph* entitled “Preparing a standard Product Monograph”.

## **2.1 Title Page**

The title page should be presented in the following format.

### **PRODUCT MONOGRAPH**

<Scheduling Symbol> <**BRAND NAME**>

<Proper name>

<Dosage Form(s) and Strength(s)>

<Pharmaceutical standard (if applicable)>

<Therapeutic Classification>

<Sponsor Name>  
<Sponsor Address>

Date of Preparation  
<MON DD, YYYY>  
or  
Date of Revision:  
<MON DD, YYYY>

Submission Control No: <control number> [optional]

## **2.2 Table of Contents**

The product monograph should include a table of contents with page numbers.

*See Guidance for Industry: Product Monograph.*

### 3 PART I: HEALTH PROFESSIONAL INFORMATION

The following heading should precede this section of the Product Monograph.

<PROPRIETARY OR BRAND NAME>

<proper name>

#### PART I: HEALTH PROFESSIONAL INFORMATION

##### 3.1 SUMMARY PRODUCT INFORMATION

*See Guidance for Industry: Product Monograph.*

In tabular format, provide:

- the route of administration of the drug;
- the dosage form(s) and strength(s) of the drug;
- a list of all clinically relevant nonmedicinal ingredients

##### 3.2 INDICATIONS AND CLINICAL USE

*See Guidance for Industry: Product Monograph.*

This section should include a list of indications supported by results of adequately controlled multicentre studies with sufficient number of patients that received <Brand Name> for an appropriate period of time.

If osteoporosis prevention and/or treatment are claimed as indications, it should be mentioned that <Brand Name> is to be considered in light of other available therapies (*see Boxed Warnings*). A clear statement declaring that adequate diet, calcium and vitamin D intake, cessation of smoking as well as regular physical weight-bearing exercise are required in addition to the administration of the proposed drug should be included.

*Note: If <Brand Name> is an estrogen-only product, state that <Brand Name> should be prescribed with an appropriate dosage of a progestin for women with intact uteri, in order to prevent endometrial hyperplasia/carcinoma.*

*If <Brand Name> is an estrogen + progestin or progestin-only product, state that <Brand Name> should be prescribed only to women with intact uteri.*

### 3.3 CONTRAINDICATIONS

*See Guidance for Industry: Product Monograph.*

The point form list of Contraindications should include the following:

- 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 or suspected estrogen-dependent or progestin-dependent malignant neoplasia (e.g. endometrial cancer).

***Note: If <Brand Name> is an estrogen-only product, the bulleted point above may be revised as follows, in consultation with Health Canada:***

Known or suspected estrogen-dependent malignant neoplasia (e.g. endometrial cancer).

- Endometrial hyperplasia (*Note: If <Brand Name> is a progestin-only product, this bulleted point may be deleted in consultation with Health Canada.*)
- 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.
- Add any other conditions where <Brand Name> should not be used.

### 3.4 WARNINGS AND PRECAUTIONS

#### 3.4.1 *Serious Warnings and Precautions Box*

The following boxed warning should be included at the beginning of this section:

<b>Serious Warnings and Precautions</b>
<p>The Women's Health Initiative (WHI) trial examined the health benefits and risks of oral combined <i>estrogen plus progestin</i> therapy (n=16,608) and oral <i>estrogen-alone</i> therapy (n=10,739) in postmenopausal women aged 50 to 79 years.<sup>1-3</sup></p> <p>The <i>estrogen plus progestin</i> arm of the WHI trial (mean age 63.3 years) indicated an increased risk of <i>myocardial infarction (MI)</i>, <i>stroke</i>, <i>invasive breast cancer</i>, <i>pulmonary emboli</i> and <i>deep vein thrombosis</i> in postmenopausal women receiving treatment with combined conjugated equine estrogens (CEE, 0.625 mg/day) and medroxyprogesterone acetate (MPA, 2.5 mg/day) for 5.2 years compared to those receiving placebo.<sup>1</sup></p> <p>The <i>estrogen-alone</i> arm of the WHI trial (mean age 63.6 years) indicated an increased risk of <i>stroke</i> and <i>deep vein thrombosis</i> in hysterectomized women treated with CEE-alone (0.625 mg/day) for 6.8 years compared to those receiving placebo.<sup>2</sup></p> <p>Therefore, the following should be given serious consideration at the time of prescribing:</p> <ul style="list-style-type: none"><li>• Estrogens with or without progestins <b>should not</b> be prescribed for primary or secondary prevention of cardiovascular diseases.</li><li>• Estrogens with or without progestins should be prescribed at <b>the lowest effective dose</b> for the approved indication.</li><li>• Estrogens with or without progestins should be prescribed for <b>the shortest period</b> possible for the approved indication.</li></ul> <p><i>(Note: If osteoporosis prevention and/or treatment are claimed/approved as indications, it should be mentioned in this warning box as an additional bulleted point that the product is to be considered in light of other available therapies.)</i></p>

*Note: If <Brand Name> is a progestin-only product, the following statement should be included immediately after the boxed warning:*

Some of the information presented in the Warnings and Precautions section is provided in light of the fact that a progestin medication is often prescribed concomitantly with an estrogen medication. Information in this section pertaining to combined estrogen-progestin therapy may therefore not apply to progestin-only therapy. Physician discretion is advised.

The following **Warnings and Precautions** subsections should be included:

### 3.4.2 *Carcinogenesis and Mutagenesis*

#### ***Breast cancer***

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

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

- 8 more cases of invasive breast cancer (38 on combined HRT versus 30 on placebo).<sup>1</sup>

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

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

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

**Note:** *If <Brand Name> is an estrogen-only product, the sentence above may be revised as follows, in consultation with Health Canada:*

It is recommended that estrogens 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).

**Note: If <Brand Name> is an estrogen-only product, the sentence above may be revised as follows, in consultation with Health Canada:**

There is a need for caution in prescribing estrogens for women with known risk factors associated with the development of breast cancer, such as strong family history of breast cancer (first degree relative) or who present a breast condition with an increased risk (abnormal mammograms and/ or atypical hyperplasia at breast biopsy).

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

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

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

*Instructions for regular self-examination of the breasts should be included in this counselling. (Note: This text should be underlined.)*

### ***Endometrial hyperplasia & endometrial carcinoma***

*Note: If <Brand Name> is a progestin-only product, this section may be modified as appropriate, in consultation with Health Canada.*

*If <Brand Name> is an estrogen-only product, include a statement indicating that estrogen-only HRT increases the risk of endometrial hyperplasia/carcinoma if taken by women with intact uteri. State that estrogen should be prescribed with an appropriate dosage of a progestin for women with intact uteri in order to prevent endometrial hyperplasia/carcinoma.*

*If <Brand Name> is an estrogen + progestin product, state that the role of a progestin, when combined with estrogen, is to prevent endometrial hyperplasia/carcinoma in women with intact uteri.*



Detailed information about occurrence of endometrial hyperplasia or endometrial malignancy should be provided with reference to data from adequate clinical studies.

### **3.4.3 Cardiovascular**

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

#### ***WHI trial findings***

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

- 8 more cases of stroke (29 on combined HRT versus 21 on placebo)
- 7 more cases of CHD ( 37 on combined HRT versus 30 on placebo).<sup>1</sup>

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

- 12 more cases of stroke (44 on *estrogen-alone* therapy versus 32 on placebo)
- no statistically significant difference in the rate of CHD.<sup>2</sup>

#### ***HERS and HERS II findings***

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

From the original HERS trial, 2321 women consented to participate in an open label extension of HERS known as HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. After 6.8 years, hormone therapy did not reduce the risk of cardiovascular events in women with CHD.<sup>5</sup>

### ***Blood pressure***

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

## **3.4.4 Endocrine and Metabolism**

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

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

Women with familial hyperlipidemias or porphyria need special surveillance. Lipid-lowering measures are recommended additionally, before treatment is started.

### ***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.

***Note: If <Brand Name> is an estrogen-only product, the sentence above may be revised as follows, in consultation with Health Canada:***

Because the prolonged use of estrogens influences the metabolism of calcium and phosphorus, estrogens should be used with caution in patients with metabolic and malignant bone diseases associated with hypercalcemia and in patients with renal insufficiency.

### ***Hypothyroidism***

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

## **3.4.5 Genitourinary**

### ***Vaginal bleeding***

Abnormal vaginal bleeding, due to its prolongation, irregularity or heaviness, occurring during therapy should prompt appropriate diagnostic measures to rule out the possibility of uterine malignancy and the treatment should be re-evaluated.

### ***Uterine leiomyomata***

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

### ***Endometriosis***

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

## **3.4.6 Hematologic**

### ***Venous thromboembolism***

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

In the *estrogen plus progestin* arm of the WHI trial, among 10,000 women on combined HRT over a one-year period, there were 18 more cases of venous thromboembolism, including 8 more cases of pulmonary embolism.<sup>1</sup>

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

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

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

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

**Note: If <Brand Name> is an estrogen-only product, the sentence above may be revised as follows, in consultation with Health Canada:**

If feasible, estrogens should be discontinued at least 4 weeks before major surgery which may be associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

### **3.4.7 Hepatic/Biliary/Pancreatic**

#### **Gallbladder diseases**

*(Note: If <Brand Name> is a progestin-only product, this section may be modified as appropriate, in consultation with Health Canada.)*

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

#### **Jaundice**

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

### ***Liver function tests***

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

## **3.4.8 Neurologic**

### ***Cerebrovascular insufficiency***

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

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

### ***Dementia***

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

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

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

- 23 more cases of probable dementia (45 on combined HRT versus 22 on placebo).<sup>6</sup>

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

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

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

- 18 more cases of probable dementia (41 on *estrogen plus progestin* or *estrogen-alone* versus 23 on placebo).<sup>7</sup>

### 3.4.9 Renal

#### *Fluid retention*

Estrogens with or without progestins may cause fluid retention.

**Note:** *If <Brand Name> is an estrogen-only product, the sentence above may be revised as follows, in consultation with Health Canada:*

Estrogens may cause fluid retention.

Therefore, particular caution is indicated in cardiac or renal dysfunction, epilepsy or asthma. If, in any of the above-mentioned conditions, a worsening of the underlying disease is diagnosed or suspected during treatment, the benefits and risks of treatment should be reassessed based on the individual case.

### 3.4.10 Special Populations

This section will be specific for the proposed product.

Add other Warnings and Precautions related to <Brand Name>.

*See Guidance for Industry: Product Monograph.*

### 3.4.11 Monitoring and Laboratory Tests

Before <Brand Name> 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. (Note: This text should be underlined.)*

### 3.5 ADVERSE REACTIONS

#### 3.5.1 Adverse Drug Reaction Overview

*See Guidance for Industry: Product Monograph.*

The following information should appear in this subsection:

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:

*(Note: If <Brand Name> is a progestin-only product, this section may be modified as appropriate, in consultation with Health Canada.)*

#### **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; haemorrhagic eruption; loss of scalp hair; hirsutism and acne.

### **Vascular disorders**

Isolated cases of: thrombophlebitis; thromboembolic disorders.

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

*See Guidance for Industry: Product Monograph.*

The following paragraph should appear at the beginning of this section:

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.

Include detailed information regarding the incidence of suspected or diagnosed cases of serious adverse events that were detected during clinical trials. This information should be presented in a tabular format and followed by a narrative discussion to explain or supplement the information provided in the table.

Information should include:

- trial duration
- active ingredient(s) and dose received
- size of group receiving the specific dose
- time point when diagnosis was first made
- radiological and histological diagnosis, as well as other diagnostic measures as applicable
- follow-up and outcome of those cases

### **3.5.3 Less Common Clinical Trial Adverse Drug Reactions**

See *Guidance for Industry: Product Monograph*.

This section should present clinical trial adverse reactions with a frequency cut off of <1%. Information should be presented as a listing and categorized by body system.

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

See *Guidance for Industry: Product Monograph*.

Indicate any clinically significant changes in laboratory values identified during clinical trials. Present data in tabular format and list laboratory parameters in alphabetical order.

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

See *Guidance for Industry: Product Monograph*.

If applicable, list all post-market adverse drug reactions.

The following statement should be included at the end of the Adverse Reactions section:

If adverse symptoms persist, the prescription of HRT should be re-considered. (*Note: This text should be underlined.*)

## **3.6 DRUG INTERACTIONS**

See *Guidance for Industry: Product Monograph*.

### **3.6.1 Serious Drug Interactions Box**

#### **Serious Drug Interactions**

Any serious, life-threatening drug interactions should be included in this box.

### **3.6.2 Overview**

In this section, provide information on any interactions based on the pharmacokinetic or pharmacologic profile of the drug. If possible, provide a brief statement on the potential mechanism of the potential interaction.

*(Note: If <Brand Name> is a progestin-only product, this section may be modified as appropriate, in consultation with Health Canada.)*

The following information should also appear in this section:

- Estrogens may diminish the effectiveness of anticoagulant, antidiabetic and antihypertensive agents.
- Preparations inducing liver enzymes (e.g. barbiturates, hydantoins, carbamazepine, meprobamates, phenylbutazone or rifampicin) may interfere with the activity of orally administered estrogens.

### **3.6.3 Drug-Drug Interactions**

*See Guidance for Industry: Product Monograph.*

Include information about drug interactions with other drug classes often used concomitantly with HRT, including but not limited to: anticonvulsants, antibiotics, anticoagulants, antihypertensives, lipid-lowering and cardiovascular medications, hypoglycemic agents, psychotropics, analgesics and other hormonal products.

### **3.6.4 Drug-Food Interactions**

*See Guidance for Industry: Product Monograph.*

State any known or potential interactions of <Brand Name> with food or beverages (e.g. grapefruit juice, caffeine) and practical guidance for the health professional, if applicable.

### **3.6.5 Drug-Herb Interactions**

*See Guidance for Industry: Product Monograph.*

The following information should appear in this section:

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.

### 3.6.6 Drug-Laboratory Test Interactions

See *Guidance for Industry: Product Monograph*.

(Note: If <Brand Name> is a progestin-only product, this section may be modified as appropriate, in consultation with Health Canada.)

The following information should appear in this section:

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 (T<sub>4</sub>) as measured by column or radioimmunoassay; T<sub>3</sub> resin uptake is decreased, reflecting the elevated TBG; free T<sub>4</sub> concentration is unaltered;
- other binding proteins may be elevated in serum 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;

Indicate whether in clinical trials with <Brand Name>, any effect on fibrinogen, antithrombin III, TBG, CBG, SHBG, protein C system (protein C/S) or activated protein C resistance (APC resistance) due to factor V Leiden mutation was seen.

The following two sentences should appear at the end of this section:

- The results of the above laboratory tests should not be considered reliable unless therapy has been discontinued for two to four weeks.
- The pathologist should be informed that the patient is receiving hormone replacement therapy (HRT) when relevant specimens are submitted.

### **3.6.7 Drug-Lifestyle Interactions**

See *Guidance for Industry: Product Monograph*.

If applicable, state any interactions of <Brand Name> with lifestyle choices (e.g. smoking).

## **3.7 DOSAGE AND ADMINISTRATION**

See *Guidance for Industry: Product Monograph*.

The dosage and administration, based on supporting clinical data from trials with <Brand Name>, should be clearly described. When appropriate, diagrams and illustrations should be used.

The Dosage and Administration section should include the following subsections as described in the revised *Guidance for Industry: Product Monograph*:

- **Dosing Considerations**
- **Recommended Dose and Dosage Adjustment**
- **Missed Dose**
- **Administration**

The recommended administration of a dose with respect to time of day and food should be indicated.

*Note: If <Brand Name> is an estrogen-only product, state that <Brand Name> should be prescribed with an appropriate dosage of a progestin for women with intact uteri in order to prevent endometrial hyperplasia/carcinoma. State that progestin therapy is not required as part of hormone replacement therapy in women who have had a previous hysterectomy.*

## **3.8 OVERDOSAGE**

The following information should appear in this section:

### **Symptoms of overdose**

*Note: This section may be revised in consultation with Health Canada, depending on the availability of product-specific information.*

Numerous reports of ingestion of large doses of estrogen products and estrogen-containing oral contraceptives by young children have not revealed acute serious ill effects. Over dosage with estrogen may cause nausea, breast discomfort, fluid retention, bloating or vaginal bleeding in women. (*Note: If <Brand Name> is a progestin-only product, this paragraph may be omitted.*)

Progestin (e.g. norethindrone acetate) overdosage has been characterized by depressed mood, tiredness, acne and hirsutism. (*Note: If <Brand Name> is an estrogen-only product, this paragraph may be omitted.*)

### **Treatment of overdose**

Explain measures to be taken in case of overdose.

Symptomatic treatment should be given.

## **3.9 ACTION AND CLINICAL PHARMACOLOGY**

This section should include a concise synopsis of the salient features of the drug's mechanisms of action, pharmacodynamics and pharmacokinetics. The information should have a demonstrated relevance to the pharmacology or pharmacodynamics of the drug in humans. This section is expected to provide concise basic information and data supported by evidence included in the New Drug Submission (NDS). This section is expected to be specific for the proposed product.

This section should include the following subsections as described in the revised *Guidance for Industry: Product Monograph*:

- **Mechanism of Action**
- **Pharmacodynamics**
- **Pharmacokinetics** [Include information on the absorption, distribution, metabolism (including metabolic pathways) and excretion (fate of absorbed components and metabolites) of the product.]
- **Special Populations and Conditions**

### **Estrogen pharmacology**

*Note: If <Brand Name> is a progestin-only product, this section may be omitted.*

Include information on estrogen pharmacology with specific reference to the type of estrogen proposed (17- $\beta$  estradiol, conjugated estrogens, ethinyl estradiol, etc).

On the basis of results from well designed dose-ranging studies, explain and justify the recommended dose of estrogen for the approved indication(s).

Discuss the necessity for protection against endometrial hyperplasia during long-term therapy in women with intact uteri. Present the clinical studies applicable to this estrogen that address the prevention of endometrial hyperplasia.

### **Progestin pharmacology**

*Note: If <Brand Name> is an estrogen-only product, this section may be omitted.*

Provide a summary of progestin pharmacology with precise reference to the type of progestin in <Brand Name> (norethindrone acetate, medroxyprogesterone acetate etc.).

Explain the purpose of estrogen combination with a progestin. Clarify that progestin is added for protection against endometrial hyperplasia during long-term therapy of women with intact uteri. On the basis of results from well-designed dose-ranging studies, explain and justify the recommended dosage of progestin to be combined with the estrogen.

The description of clinical pharmacology should indicate the targeted population for which the drug is indicated.

Include data supporting clinical pharmacology, e.g. effects on:

- vasomotor symptoms due to estrogen deficiency
- osteoporosis/osteopenia
- urogenital symptoms
- metabolism (lipid profile, carbohydrate, and liver function tests)
- hemostatic factors (effect on coagulation factors and coagulation tests).

Discuss the occurrence of uterine bleeding including amount, duration, frequency, and cyclicity (if appropriate, provide graphic diagram).

The above information should be available for each of the active ingredient(s) and each proposed dosage regimen when applicable.

### **3.10 STORAGE AND STABILITY**

*See Guidance for Industry: Product Monograph.*

This section should specify the recommended storage conditions for each dosage form. Include information on storage temperature, light exposure, moisture protection and other storage instructions.

### **3.11 SPECIAL HANDLING INSTRUCTIONS**

*See Guidance for Industry: Product Monograph.*

Specify any special handling instructions for <Brand Name>.

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

*See Guidance for Industry: Product Monograph.*

Describe in this section all available marketed dosage forms, strengths and routes of administration. For each strength of each dosage form of the product, provide an alphabetical listing of all nonmedicinal ingredients, using the common or proper name.

A description of the type and size of all available marketing packing formats should be included, in addition to any additional packaging information that may impact on patient safety.



## **4 PART II: SCIENTIFIC INFORMATION**

### **4.1 PHARMACEUTICAL INFORMATION**

*See Guidance for Industry: Product Monograph.*

#### **Drug Substance**

Provide the following information on the drug substance:

- Proper name
- Chemical name
- Molecular formula and molecular mass
- Structural formula
- Relevant physicochemical properties

### **4.2 CLINICAL TRIALS**

*See Guidance for Industry: Product Monograph.*

This section of the product monograph should describe pivotal studies that support the efficacy and safety of <Brand Name> and should be presented in a tabular format.

For each clinical trial, indicate the number of participating subjects that used <Brand Name> as well as the drop-out rate. Also indicate the time length of each trial, major conclusions and any serious complications.

In a controlled trial, specify the drug used for comparison and confirm its availability in Canada.

This section should also include comparative bioavailability studies, as required, for revised formulation and new dosage forms. Link differences, if any, between the formulation(s) used in the clinical trials and the marketed formulations. Specify which formulation is tested in each clinical trial.

All clinical studies cited in this section must be annotated to a reference to allow users of the product monograph to seek out detailed information as required.

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

See *Guidance for Industry: Product Monograph*.

#### **4.2.2 Pivotal Comparative Bioavailability Studies**

See *Guidance for Industry: Product Monograph*.

### **4.3 DETAILED PHARMACOLOGY**

See *Guidance for Industry: Product Monograph*.

### **4.4 MICROBIOLOGY (if applicable)**

See *Guidance for Industry: Product Monograph*.

### **4.5 TOXICOLOGY**

See *Guidance for Industry: Product Monograph*.

### **4.6 REFERENCES**

See *Guidance for Industry: Product Monograph*.

The following references should be included in this section:

1. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. Principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002; 288(3):321-333.
2. The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. The Women's Health Initiative randomized controlled trial. *JAMA*. 2004; 291(14):1701 – 1712.
3. Chlebowski RT, Hendrix SL, Langer RD, Stefanick ML, Gass M, Lane D, et al. The Women's Health Initiative randomized trial. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women. *JAMA*. 2003; 289(24):3243-3253.
4. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, et al for the Heart and Estrogen/progestin Replacement Study (HERS) Research Group. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA*. 1998; 280(7):605-613.

5. Grady D, Herrington D, Bittner V, Blumenthal R, Davidson M, Hlatky M, et al for the HERS Research Group. Cardiovascular disease outcomes during 6.8 years of hormone therapy. Heart and Estrogen/progestin Replacement Study follow-up (HERS II). JAMA. 2002; 288(1):49-57.
6. Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JK, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women. The Women's Health Initiative Memory Study: A randomized controlled trial. JAMA. 2003; 289(20):2651-2662.
7. Shumaker SA, Legault C, Kuller L, Rapp SR, Thal L, Lane DS, et al. Conjugated Equine Estrogens and Incidence of Probable Dementia and Mild Cognitive Impairment in Postmenopausal Women. Women's Health Initiative Memory Study. JAMA. 2004; 291(24):2947-2958.

## 5 PART III: CONSUMER INFORMATION

The following heading should precede this section of the Product Monograph.

*See also Guidance for Industry: Product Monograph.*

### PART III: CONSUMER INFORMATION

<Brand Name>

<Proper Name>

Consumer Information is a lay-language translation of information contained in Parts I and II of the product monograph. It should contain information that is required by the patient for safe and effective use of <Brand Name>. It should describe when and how to use the product and outline the risks and benefits of the treatment. Where appropriate, in order to facilitate understanding, diagrams and illustrations should be used.

#### **IMPORTANT: PLEASE READ**

The following paragraph should be included in this section:

This leaflet is part III of a three-part “Product Monograph” published when <Brand Name> was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about <Brand Name>. Contact your doctor or pharmacist if you have any questions about the drug.

#### **5.1 ABOUT THIS MEDICATION**

##### **What the medication is used for:**

Provide a point form listing from the Indications section of Part I. If the Indications section includes lifestyle recommendations as part of the therapy, they should be included here.

If osteoporosis prevention and/or treatment are claimed/approved as indications, it should be mentioned in this section that the product is to be considered in light of other available therapies. A statement should be included advising the consumer to discuss adequate diet, calcium and vitamin D intake, cessation of smoking and regular physical weight-bearing exercise with her doctor or pharmacist in addition to the administration of the proposed drug.

*Note: If <Brand Name> is an estrogen-only product, include a statement indicating that it should not be used by women with intact uteri unless it is prescribed in association with a progestin.*

The following two paragraphs should then be included:

<Brand Name> should be used only under the supervision of a doctor, with regular follow-up at least once a year to identify side effects associated with its use. Your first follow-up visit should be within 3 to 6 months of starting treatment. Your visit may include a blood pressure check, a breast exam, a Pap smear and pelvic exam. You should have a mammogram before starting treatment and at regular intervals as recommended by your doctor. Your doctor may recommend some blood tests.

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

**What it does:**

From the Action and Clinical Pharmacology section of Part I, provide a brief lay explanation of the mechanism of action of the drug. From the Action and Clinical Pharmacology section of Part I and Clinical Trials section of Part II, indicate how long it takes to work and how one knows if it is working.

**When it should not be used:**

Provide a point form listing from the Contraindications section of Part I.

**What the medicinal ingredient(s) is/are :**

Provide the proper name(s) or common name(s).

**What the nonmedicinal ingredients are :**

Provide an alphabetical listing of all of the nonmedicinal ingredients, as provided in the Dosage Forms, Composition and Packaging section of Part I.

**What dosage form it comes in:**

From the Dosage Forms, Composition and Packaging section of Part I, provide the available marketed dosage forms and strengths. List the name of the dosage form followed by the strengths in increasing order.

## 5.2 WARNINGS AND PRECAUTIONS

The following boxed warning should be included at the beginning of this section:

<b>Serious Warnings and Precautions</b>
<p>The Women's Health Initiative (WHI) trial is a large clinical study that assessed the benefits and risks of oral combined <i>estrogen plus progestin</i> therapy and oral <i>estrogen-alone</i> therapy compared with placebo (a pill with no active ingredients) in postmenopausal women.</p> <p>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 <i>estrogen plus progestin</i>.</p> <p>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 <i>estrogen-alone</i>.</p> <p>Therefore, you should highly consider the following:</p> <ul style="list-style-type: none"><li>• 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.</li><li>• There is an increased risk of stroke and blood clots in the large veins with the use of estrogen-alone therapy.</li><li>• Estrogens with or without progestins should not be used for the prevention of heart disease or stroke.</li><li>• Estrogens with or without progestins should be used at <b>the lowest effective dose</b> and for <b>the shortest period of time</b> possible. Regular medical follow-up is advised.</li></ul>

The following **Warnings and Precautions** subsections should be included:

### ***Breast Cancer***

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

The results of the WHI trial indicated no difference in the risk of breast cancer in post-menopausal 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.

***Note: If <Brand Name> is an estrogen-only product, the sentence above may be revised as follows, in consultation with Health Canada:***

Estrogens 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 technique for breast self-examination with your doctor.

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

*(Note: If <Brand Name> is a progestin-only product, this section may be modified as appropriate, in consultation with Health Canada.)*

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

***Note: If <Brand Name> is an estrogen + progestin product, the following sentence should appear in this location:***

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

**Note: If <Brand Name> is an estrogen-only product, the following sentence should appear in this location:**

If you still have your uterus, you should take a progestin medication (another hormone drug) regularly for a certain number of days of each month 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.

### ***Heart Disease and Stroke***

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

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

### ***Abnormal Blood Clotting***

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

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

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



### ***Gallbladder Disease***

*(Note: If <Brand Name> is a progestin-only product, this section may be modified as appropriate, in consultation with Health Canada.)*

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 substudy 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 <Brand Name> talk to your doctor or pharmacist if you:**

- have a history of allergy or intolerance to any medications or other substances
- have a personal history of breast disease (including breast lumps) and/or breast biopsies, or a family history of breast cancer
- have experienced any unusual or undiagnosed vaginal bleeding
- have a history of uterine fibroids or endometriosis
- have a history of liver disease, jaundice (yellowing of the eyes and/or skin) or itching related to estrogen use or during pregnancy
- have a history of migraine headache
- 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 a history of bone disease (this includes certain metabolic conditions or cancers that can affect blood levels of calcium and phosphorus)
- have been diagnosed with diabetes
- have been diagnosed with porphyria (a disease of blood pigment)
- have a history of high cholesterol or high triglycerides
- are pregnant or may be pregnant
- have had a hysterectomy (surgical removal of the uterus)
- smoke

### 5.3 INTERACTIONS WITH THIS MEDICATION

This section is to ensure that consumers are aware of any medications, foods or beverages (e.g alcohol) known to interact with this medication. Serious or significant interactions should be listed (e.g. drug interactions listed in the Serious Drug Interactions box in Part I).

The following statement should be included:

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

### 5.4 PROPER USE OF THIS MEDICATION

Provide information on how to prepare or administer the drug or operate a device.

#### **Usual dose:**

From the Dosage and Administration section of Part I, provide the typical dose, when to take it and how to take it.

#### **Overdose:**

From the Overdosage section of Part I, provide information on what to do if the individual takes too much medication. This includes overdose with a single dose or with cumulative dosing.

### **Missed Dose:**

From the Dosage and Administration section of Part I, provide information on what to do if a dose is missed.

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

This section should include a brief summary of the self-limiting and serious side effects and the action consumers should take when experiencing them. The information to be included will be determined in consultation with the sponsor and Health Canada.

This section should include the incidence of the following adverse effects encountered during clinical trials:

- Genital bleeding/spotting
- Headache
- Breast tenderness
- Bloating
- Weight gain
- Others

Describe what is to be expected during long-term use of <Brand Name>.

### ***Text***

*See Guidance for Industry: Product Monograph.*

Self-limiting side effects should be described in narrative format. Self-limiting side effects are considered to be those that generally don't require medical attention and will usually go away as the body adjusts to the drug. The effects should be grouped by frequency using the terminology provided by the Council for International Organizations of Medical Sciences (CIOMS) (e.g., common, rare, etc.). A statement of the risk of dependency, if applicable, should be included here.

**Table**

See *Guidance for Industry: Product Monograph*.

Serious side effects should be included in a table. Whether the patient can do something about the effect should be used as the criteria for including side effects in the table. The side effects should be grouped by frequency using the CIOMS terminology. Within each group the effects should be listed alphabetically. For serious side effects, instructions to discontinue the use of the product (if safe to do so) should be provided.

The table should always follow the text.

The table should include the following serious side effects. Additional serious side effects to be included in the table should be determined in consultation with Health Canada.

<b>SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM</b>				
<Frequency (common or uncommon)>	Symptom/possible side effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
	Abdominal pain, nausea or vomiting		✓	
	Breast lump		✓	
	Crushing chest pain or chest heaviness			✓
	Pain or swelling in the leg			✓
	Persistent sad mood			✓
	Sharp pain in the chest, coughing blood or sudden shortness of breath			✓

	Sudden partial or complete loss of vision			✓
	Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech or weakness or numbness in an arm or leg			✓
	Unexpected vaginal bleeding		✓	
	Yellowing of the skin or eyes (jaundice)			✓

The following statement should be included at the end of the side effects section:

This is not a complete list of side effects. For any unexpected effects while taking <Brand Name>, contact your doctor or pharmacist.

## 5.6 HOW TO STORE IT

This section should include a brief summary of the information provided in the Storage Instructions section of Part I.

The following statement should be included for all products:

Keep out of reach of children.

## 5.7 REPORTING SUSPECTED SIDE EFFECTS

The following box on reporting suspected adverse drug reactions should be included in this section:

## **REPORTING SUSPECTED SIDE EFFECTS**

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

**toll-free telephone: 866-234-2345**

**toll-free fax: 866-678-6789**

**By email: [cadrmc@hc-sc.gc.ca](mailto:cadrmc@hc-sc.gc.ca)**

**By regular mail:**

**Canadian Adverse Drug Reaction Monitoring Program (CADRMP)**

**Marketed Health Products Directorate**

**Health Canada**

**Tunney's Pasture, Address Locator: 0701C**

**Ottawa ON, K1A 0K9**

*NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.*

## **5.8 MORE INFORMATION**

For general instructions on the information contained in Part III, where to find the full product monograph and how to contact the sponsor, the following or similar statement should be included:

This document plus the full product monograph prepared for health professionals can be found at <http://www.website.document> or by contacting the sponsor, <Sponsor Name>, at 1-800-XXX-XXXX.

This leaflet was prepared by <Sponsor Name>

## **5.9 DATE**

Last revised: <MON DD, YYYY>