PHARMACY AND POISONS BOARD
HONG KONG
香港藥劑業及毒藥管理局

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貴處檔號

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24th December 2021

To: Certificate holders of
registered pharmaceutical products

Dear Sir / Madam,

New Warnings for Hormone Replacement Therapy (HRT)

On 13th December 2021, the Pharmacy and Poisons (Registration of Pharmaceutical Products and Substances: Certification of Clinical Trial/Medicinal Test) Committee (the Committee) considered the latest new warnings related to the risk of breast cancer for HRT products by the drug regulatory authorities of the European Union, Singapore and the United Kingdom, and decided that the sales pack labels and / or package inserts of relevant registered HRT products should include the following new safety information (or equivalent) as appropriate:

(I) For combined estrogen[1]-progestogen HRT products

Special warnings and precautions for use

Breast Cancer

[1] Examples of estrogens include chlorotrianisene, conjugated estrogens, dienestrol, diethylstilbestrol, estradiol, estriol, estrone, ethinylestradiol, methallenestril, moxestrol and promestriene, etc.

The overall evidence shows an increased risk of breast cancer in women taking combined estrogen-progestogen or estrogen-only HRT that is dependent on the duration of taking HRT.

The randomised placebo-controlled trial, the Women's Health Initiative study (WHI), and a meta-analysis of prospective epidemiological studies are consistent in finding an increased risk of breast cancer in women taking combined estrogen-progestogen HRT that becomes apparent after about 3 (1-4) years.

Results from a large meta-analysis showed that after stopping treatment, the excess risk will decrease with time and the time needed to return to baseline depends on the duration of prior HRT use. When HRT was taken for more than 5 years, the risk may persist for 10 years or more.

HRT, especially estrogen-progestogen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

Undesirable effects

Breast cancer risk

An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined estrogen-progestogen therapy for more than 5 years.

The increased risk in users of estrogen-only therapy is lower than that seen in users of estrogen-progestogen combinations.

The level of risk is dependent on the duration of use.

Absolute risk estimations based on results of the largest randomised placebo-controlled trial (WHI-study) and the largest meta-analysis of prospective epidemiological studies are presented.

Largest meta-analysis of prospective epidemiological studies

Estimated additional risk of breast cancer after 5 years' use in women with BMI 27 (kg/m^2)

Age at start HRT (years)	*Incidence per 1,000 never-users of HRT over a 5 year period (50-54 years)**	*Risk ratio*	*Additional cases per 1,000 HRT users after 5 years*
Estrogen-only HRT			

50	13.3	1.2	2.7
Combined estrogen-progestogen			
50	13.3	1.6	8.0

** Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m^2).*

Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.

Estimated additional risk of breast cancer after 10 years' use in women with BMI 27 (kg/m^2)

Age at start HRT (years)	Incidence per 1,000 never-users of HRT over a 10 year period (50-59 years)*	Risk ratio	Additional cases per 1,000 HRT users after 10 years
Estrogen-only HRT			
50	26.6	1.3	7.1
Combined estrogen-progestogen			
50	26.6	1.8	20.8

** Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m^2).*

Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.

US WHI Studies – additional risk of breast cancer after 5 years' use

Age range (years)	Incidence per 1,000 women in placebo arm over 5 years	Risk ratio & 95% CI	Additional cases per 1,000 HRT users over 5 years (95% CI)
CEE estrogen-only			
50-79	21	0.8 (0.7-1.0)	-4 (-6 – 0)*
CEE+MPA estrogen & progestogen**			
50-79	17	1.2 (1.0-1.5)	4 (0-9)

**WHI study in women with no uterus, which did not show an increase in risk of breast cancer.*

*** When the analysis was restricted to women who had not used HRT prior*

to the study there was no increased risk apparent during the first 5 years of treatment: after 5 years the risk was higher than in non-users.

(II) **For estrogen-only HRT products**

Special warnings and precautions for use

Breast Cancer

The overall evidence shows an increased risk of breast cancer in women taking combined estrogen-progestogen or estrogen-only HRT that is dependent on the duration of taking HRT.

The Women's Health Initiative trial (WHI) found no increase in the risk of breast cancer in hysterectomised women using estrogen-only HRT. Observational studies have mostly reported a small increase in risk of having breast cancer diagnosed that is lower than that found in users of estrogen-progestogen combinations.

Results from a large meta-analysis showed that after stopping treatment, the excess risk will decrease with time and the time needed to return to baseline depends on the duration of prior HRT use. When HRT was taken for more than 5 years, the risk may persist for 10 years or more.

HRT, especially estrogen-progestogen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

Undesirable effects

Breast cancer risk

An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined estrogen-progestogen therapy for more than 5 years.

The increased risk in users of estrogen-only therapy is lower than that seen in users of estrogen-progestogen combinations.

The level of risk is dependent on the duration of use.

Absolute risk estimations based on results of the largest randomised placebo-controlled trial (WHI-study) and the largest meta-analysis of prospective epidemiological studies are presented.

Largest meta-analysis of prospective epidemiological studies

Estimated additional risk of breast cancer after 5 years' use in women with BMI 27 (kg/m²)

Age at start HRT (years)	*Incidence per 1,000 never-users of HRT over a 5 year period (50-54 years)**	*Risk ratio*	*Additional cases per 1,000 HRT users after 5 years*
Estrogen-only HRT			
50	*13.3*	*1.2*	*2.7*
Combined estrogen-progestogen			
50	*13.3*	*1.6*	*8.0*

** Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m²).*

Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.

Estimated additional risk of breast cancer after 10 years' use in women with BMI 27 (kg/m²)

Age at start HRT (years)	*Incidence per 1,000 never-users of HRT over a 10 year period (50-59 years)**	*Risk ratio*	*Additional cases per 1,000 HRT users after 10 years*
Estrogen-only HRT			
50	*26.6*	*1.3*	*7.1*
Combined estrogen-progestogen			
50	*26.6*	*1.8*	*20.8*

** Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m²).*

Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.

US WHI Studies – additional risk of breast cancer after 5 years' use

Age range (years)	*Incidence per 1,000 women in placebo arm over 5 years*	*Risk ratio & 95% CI*	*Additional cases per 1,000 HRT users over 5 years (95%*

			CI)
CEE estrogen-only			
50-79	*21*	*0.8 (0.7-1.0)*	*-4 (-6 – 0)**
*CEE+MPA estrogen & progestogen***			
50-79	*17*	*1.2 (1.0-1.5)*	*4 (0-9)*

**WHI study in women with no uterus, which did not show an increase in risk of breast cancer.*

*** When the analysis was restricted to women who had not used HRT prior to the study there was no increased risk apparent during the first 5 years of treatment: after 5 years the risk was higher than in non-users.*

(III) **For HRT products containing combination of conjugated estrogens and bazedoxifene**

Special warnings and precautions for use

Breast cancer

The overall evidence shows an increased risk of breast cancer in women taking estrogen-only HRT that is dependent on the duration of taking HRT.

The Women's Health Initiative (WHI) trial found no increase in the risk of breast cancer in hysterectomised women using estrogen-only therapy.

Observational studies have mostly reported a small increase in risk of having breast cancer in estrogen-only users diagnosed that is lower than that found in users of estrogen-progestogen combinations.

Results from a large meta-analysis showed that after stopping treatment, the excess risk will decrease with time and the time needed to return to baseline depends on the duration of prior HRT use. When HRT was taken for more than 5 years, the risk may persist for 10 years or more.

The effect of conjugated estrogens/bazedoxifene on the risk of breast cancer is unknown.

Undesirable effects

Breast cancer risk

Breast cancer risk associated with the use of estrogens alone is represented by several studies. The increased risk to users of estrogen-only therapy is lower than that seen in users of estrogen–progestogen combinations. The level of risk is dependent on duration of use. Absolute risk estimations based on the results of the largest randomised placebo-controlled trial (WHI-

study) and the largest meta-analysis of prospective epidemiological studies are presented.

US WHI Estrogen-only (ET) arm – additional risk of breast cancer after 5 years' use

Age range (years)	*Incidence per 1,000 women in placebo arm over 5 years*	*Risk ratio & 95% CI*	*Additional cases per 1,000 ET users over 5 years (95% CI)*
CE Estrogen-only			
50-79	*21*	*0.8 (0.7-1.0)*	*-4 (-6 – 0)**

**WHI study in women with no uterus, which did not show an increase in risk of breast cancer.*

Largest meta-analysis of prospective epidemiological studies

Estimated additional risk of breast cancer after 5 years' use in women with BMI 27 (kg/m^2)

Age at start HRT (years)	*Incidence per 1,000 never-users of HRT over a 5 year period (50-54 years)**	*Risk ratio*	*Additional cases per 1,000 HRT users after 5 years*
Estrogen-only			
50	*13.3*	*1.2*	*2.7*

** Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m^2).*

Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.

Estimated additional risk of breast cancer after 10 years' use in women with BMI 27 (kg/m^2)

Age at start HRT (years)	*Incidence per 1,000 never-users of HRT over a 10 year period (50-59 years)**	*Risk ratio*	*Additional cases per 1,000 HRT users after 10 years*

Estrogen-only			
50	*26.6*	*1.3*	*7.1*

** Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m^2).*

Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.

(IV) For HRT products containing tibolone

Special warnings and precautions for use

The risks of stroke, breast cancer and, in women with an intact uterus, endometrial cancer for each woman should be carefully assessed, in the light of her individual risk factors and bearing in mind the frequency and characteristics of both cancers and stroke, in terms of their response to treatment, morbidity and mortality.

Breast cancer

A meta-analysis of epidemiological studies, including the Million Women Study (MWS), showed a significant increase in the risk of breast cancer in association with use of the 2.5 mg dose. This risk became apparent within 3 years of use and increased with duration of intake. After stopping treatment, the excess risk will decrease with time and the time needed to return to baseline depends on the duration of prior HRT use. When HRT was taken for more than 5 years, the risk may persist for 10 years or more.

No data for persistence of risk after stopping are available for tibolone, but a similar pattern cannot be ruled out.

Undesirable effects

Breast cancer

An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined estrogen-progestogen therapy for more than 5 years.

The increased risk in users of estrogen-only and tibolone therapy is lower than seen in users of estrogen-progestogen combinations.

The level of risk is dependent on the duration of use.

Results of the largest epidemiological study (MWS) are presented.

Million Women study – Estimated additional risk of breast cancer after 5 years' use

Age range (years)	*Additional cases per 1,000 never-users of HRT over a 5 year period*	*Risk ratio & 95% CI#*	*Additional cases per 1,000 HRT users over 5 years (95% CI)*
Estrogen-only HRT			
50-65	*9-12*	*1.2*	*1-2 (0-3)*
Combined estrogen-progestogen			
50-65	*9-12*	*1.7*	*6 (5-7)*
Tibolone			
50-65	*9-12*	*1.3*	*3 (0-6)*
#Overall risk ratio. The risk ratio is not constant but will increase with increasing duration of use.			

(V) **For HRT products containing low dose estrogen for vaginal application**

Special warnings and precautions for use

The following risks have been associated with systemic HRT and apply to a lesser extent for estrogen products for vaginal application of which the systemic exposure to the estrogen remains within the normal postmenopausal range. However, they should be considered in case of long term or repeated use of this product.

Breast cancer

Epidemiological evidence from a large meta-analysis suggests no increase in risk of breast cancer in women with no history of breast cancer taking low dose vaginally applied estrogens. It is unknown if low dose vaginal estrogens stimulate recurrence of breast cancer.

You are therefore required to review and revise, if necessary, the sales pack labels and / or package inserts of the concerned products registered by your company to ensure that the products comply with the above new requirements. The revised sales pack labels and / or package inserts should be submitted to the Committee for approval within 2 months from the date of this letter. Failing to comply with the above requirements may result in de-registration of the products or registration not renewed by the Committee.

If you have any enquiries on the above issue, please contact Ms. Queenie CHAN at 3974 4147.

Yours faithfully,

(T.K. YIM)
Secretary,
Pharmacy and Poisons (Registration of Pharmaceutical Products and Substances: Certification of Clinical Trial/Medicinal Test) Committee

c.c. 7-15/3, Product Files

TK/QC