



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 11-14 May 2020 PRAC meeting

This document provides an overview of the recommendations adopted by the Pharmacovigilance Risk Assessment Committee (PRAC) on the signals discussed during the meeting of 11-14 May 2020 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT]⁵ reference numbers).

PRAC recommendations to provide supplementary information are directly actionable by the concerned marketing authorisation holders (MAHs). PRAC recommendations for regulatory action (e.g. amendment of the product information) are submitted to the Committee for Medicinal Products for Human Use (CHMP) for endorsement when the signal concerns Centrally Authorised Products (CAPs), and to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) for information in the case of Nationally Authorised Products (NAPs). Thereafter, MAHs are expected to take action according to the PRAC recommendations.

When appropriate, the PRAC may also recommend the conduct of additional analyses by the Agency or Member States.

MAHs are reminded that in line with Article 16(3) of Regulation No (EU) 726/2004 and Article 23(3) of Directive 2001/83/EC, they shall ensure that their product information is kept up to date with the current scientific knowledge including the conclusions of the assessment and recommendations published on the European Medicines Agency (EMA) website (currently acting as the EU medicines webportal).

For CAPs, at the time of publication, PRAC recommendations for update of product information have been agreed by the CHMP at their plenary meeting (25-28 May 2020) and corresponding variations will be assessed by the CHMP.

For nationally authorised medicinal products, it is the responsibility of the National Competent Authorities (NCAs) of the Member States to oversee that PRAC recommendations on signals are adhered to.

¹ Expected publication date. The actual publication date can be checked on the webpage dedicated to [PRAC recommendations on safety signals](#).

² Some minor amendments were implemented in the product information for hormone replacement therapy (HRT) on 3 August 2020.

³ A clarification was added to the buprenorphine PRAC recommendation on 1 October 2020 (see footnote 7 on page 5).

⁴ A link to the report from the CMDh meeting held on 15-16 September 2020 was added to buprenorphine PRAC recommendation on 15 October 2020 to provide further information to MAHs of serotonergic medicinal products (see footnote 8 on page 5).

⁵ The relevant EPITT reference number should be used in any communication related to a signal.



Variations for CAPs are handled according to established EMA procedures. MAHs are referred to the available [guidance](#). Variations for NAPs (including via mutual recognition and decentralised procedures) are handled at national level in accordance with the provisions of the Member States.

The timeline recommended by PRAC for submission of variations following signal assessment is applicable to both innovator and generic medicinal products, unless otherwise specified.

For procedural aspects related to the handling of PRAC recommendations on signals (e.g. submission requirements, contact points, etc.) please refer to the [Questions and Answers on signal management](#).

1. Recommendations for update of the product information⁶

1.1. Baricitinib – Diverticulitis

Authorisation procedure	Centralised
EPITT No	19496
PRAC rapporteur(s)	Adam Przybyłkowski (PL)
Date of adoption	14 May 2020

Recommendation

Having considered the available evidence, the PRAC has agreed that the MAH of baricitinib should submit a variation within 2 months from the publication of the PRAC recommendation, to amend the product information as described below (new text underlined):

Summary of product characteristics

4.4. Special warnings and precautions for use

Diverticulitis

Events of diverticulitis and gastrointestinal perforation have been reported in clinical trials and from postmarketing sources. Baricitinib should be used with caution in patients with diverticular disease and especially in patients chronically treated with concomitant medications associated with an increased risk of diverticulitis: nonsteroidal anti-inflammatory drugs, corticosteroids, and opioids. Patients presenting with new onset abdominal signs and symptoms should be evaluated promptly for early identification of diverticulitis or gastrointestinal perforation.

4.8. Undesirable effects

Gastrointestinal disorders

Frequency 'uncommon': diverticulitis

Package leaflet

2. What you need to know before you take Olumiant

[...]

Warnings and precautions

Talk to your doctor or pharmacist before and during treatment with Olumiant if you:

[...]

- have had diverticulitis (a type of inflammation of the large intestine) or ulcers in stomach or intestines (see section 4)

If you notice any of the following serious side effects, you need to tell a doctor straight away:

- severe abdominal pain especially accompanied with fever, nausea and vomiting.

⁶ Translations in all official EU languages of the new product information adopted by PRAC are also available to MAHs on the [EMA website](#).

Other medicines and Olumiant

Tell your doctor or pharmacist if you are taking, have recently taken, or might take, any other medicines. In particular, tell your doctor or pharmacist before taking Olumiant if you are taking:

- medicines that may increase your risk of diverticulitis such as a non-steroidal anti-inflammatory medicines (usually used to treat painful and/or inflammatory conditions of muscle or joints) and/or opioids (used to treat severe pain), and/or corticosteroids (usually used to treat inflammatory conditions) (see section 4).

4. Possible side effects

Uncommon side effects (may affect up to 1 in 100 people):

[...]

- Diverticulitis (painful inflammation of small pockets in the lining of your intestine)

1.2. Buprenorphine; buprenorphine, naloxone – Drug-drug interaction with serotonergic drugs leading to serotonin syndrome

Authorisation procedure	Centralised and non-centralised
EPITT No	19475
PRAC rapporteur(s)	Martin Huber (DE)
Date of adoption	14 May 2020

Recommendation

Having reviewed the MAH's responses on the risk of serotonin syndrome in association with the interaction between buprenorphine and other serotonergic drugs, the PRAC agreed that the MAH(s) of buprenorphine-containing medicinal products should submit a variation within 2 months from the publication of the PRAC recommendation to amend the product information as described below (new text underlined/text to be removed with strikethrough).

Summary of product characteristics

4.4. Special warnings and precautions for use

Serotonin syndrome

Concomitant administration of [product name] and other serotonergic agents, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).

If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

4.5. Interaction with other medicinal products and other forms of interaction

[Product name] should be used cautiously when co-administered with:

- Serotonergic medicinal products, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

Package leaflet

2. What you need to know before you take [product name]

Warnings and precautions

Talk to your doctor before taking [product name] if you have:

- Depression or other conditions that are treated with antidepressants.
The use of these medicines together with [product name] can lead to serotonin syndrome, a potentially life-threatening condition (see "Other medicines and [product name]").

Other medicines and [product name]

Tell your doctor if you are taking, have recently taken or might take any other medicines.

Some medicines may increase the side effects of [product name] and may sometimes cause very serious reactions. Do not take any other medicines whilst taking [product name] without first talking to your doctor, especially:

- anti-depressants such as moclobemide, tranylcypromine, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, duloxetine, venlafaxine, amitriptyline, doxepine, or trimipramine. These medicines may interact with [product name] and you may experience symptoms such as involuntary, rhythmic contractions of muscles, including the muscles that control movement of the eye, agitation, hallucinations, coma, excessive sweating, tremor, exaggeration of reflexes, increased muscle tension, body temperature above 38°C. Contact your doctor when experiencing such symptoms.

The MAHs of serotonergic medicinal products^{7 8} should also ensure that this possible interaction with buprenorphine/opioids is reflected in their product information.

⁷ An orientation of the concerned substances is included in the published PRAC agenda:

https://www.ema.europa.eu/en/documents/agenda/agenda-prac-draft-agenda-meeting-11-14-may-2020_en.pdf

⁸ The report from the CMDh meeting held on 15-16 September 2020 provides useful information for MAHs of serotonergic medicinal products:

[https://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/cmdh_pressreleases/2020/09_2020_CMDh_press_relea
se.pdf](https://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/cmdh_pressreleases/2020/09_2020_CMDh_press_release.pdf)

1.3. Hormone replacement therapy (HRT)⁹ – New information on the known risk of breast cancer

Authorisation procedure	Centralised and non-centralised
EPITT No	19482
PRAC rapporteur(s)	Menno van der Elst (NL)
Date of adoption	14 May 2020

Recommendation

Based on the results from the large meta-analysis published in the Lancet^[1], the PRAC considers that the study provides relevant new information regarding the known risk of breast cancer that justifies a revision of the current product information of Hormone Replacement Therapy (HRT) products.

The following updates (new text bold and underlined, deleted text strikethrough) of the CMDh Core summary of product characteristics (SmPC) and Package Leaflet (PL) for post-menopausal HRT products have been endorsed by the PRAC. The marketing authorisation holders for products containing oestrogens only and combined oestrogen-progestagen HRT products, HRT-products which are vaginally applied estrogens of which the systemic exposure remains within postmenopausal range, DUAVIVE (conjugated oestrogens/bazedoxifene) and tibolone should **submit a variation within 3 months** to amend the product information as described here below:

Proposed amendments in core SmPC and PL for oestrogen only and combined oestrogen-progestagen HRT-products

Core SmPC for HRT products

4.4. Special warnings and precautions for use

Breast cancer

The overall evidence ~~suggests~~ **shows** an increased risk of breast cancer in women taking combined oestrogen-progestagen ~~and possibly also~~ **or** oestrogen-only HRT, that is dependent on the duration of taking HRT.

Combined oestrogen-progestagen therapy

- 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 oestrogen-progestagen for HRT that becomes apparent after about 3 **(1-4)** years (see section 4.8).

Oestrogen-only therapy

- The WHI trial found no increase in the risk of breast cancer in hysterectomised women using oestrogen-only HRT. Observational studies have mostly reported a small increase in risk of having breast cancer diagnosed that is ~~substantially~~¹⁰ lower than that found in users of oestrogen-progestagen combinations (see section 4.8).

⁹ Chlorotrianisene; conjugated estrogens; conjugated estrogens, bazedoxifene; dienestrol; diethylstilbestrol; estradiol; estradiol, norethisterone; estriol; estrone; ethinylestradiol; methallenestril; moxestrol; promestriene; tibolone

^[1] Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. Lancet. 2019 Sep 28;394(10204):1159

¹⁰ "Substantially" was missing in the document initially published on 23 June 2020.

The excess risk becomes apparent within a few years of use but returns to baseline within a few (at most five) 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 oestrogen-progestagen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

4.8. Undesirable effects

Breast cancer risk

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestagen therapy for more than 5 years.
- **The** Any increased risk in users of oestrogen-only therapy is ~~substantially~~ lower than that seen in user of oestrogen-progestagen combinations.
- The level of risk is dependent on the duration of use (see section 4.4).
- **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 (MWS) are presented.

Million Women **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 range (years)	Additional cases Incidence per 1000 never-users of HRT over a 5 year period (50-54 years)*	Risk ratio & 95%CI#	Additional cases per 1000 HRT users over after 5 years (95%CI)
Oestrogen only HRT			
50-65	9-12 13.3	1.2	1-2 (0-3) 2.7
Combined oestrogen-progestagen			
50-65	9-12 13.3	1.7 1.6	6 (5-7) 8.0

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

#Overall risk ratio. The risk ratio is not constant but will increase with increasing duration on use

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)	Additional cases Incidence per 1000 never-users of HRT over a 10 year period (50-59 years) *	Risk ratio	Additional cases per 1000 HRT users after 10 years
Oestrogen only HRT			
50	26.6	1.3	6-9 7.1
Combined oestrogen-progestagen			
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 (yrs)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95%CI	Additional cases per 1000 HRT users over 5 years (95%CI)
CEE oestrogen-only			
50-79	21	0.8 (0.7 – 1.0)	-4 (-6 – 0)* [‡]
CEE+MPA oestrogen & progestagen[‡]			
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.

Core PL for HRT products

2. What you need to know before you use <product name>

Do not take X

- If you have or have ever had **breast cancer**, or if you are suspected of having it;

Breast cancer

Evidence ~~suggests~~ **shows** that taking combined oestrogen-progestogen and¹¹ ~~possibly also~~ **or** oestrogen-only **hormone replacement therapy (HRT)** increases the risk of breast cancer. The extra risk depends on how long you ~~take~~ **use** HRT. The additional risk becomes clear within a few **3** years **of use**. However, it returns to normal within a few years (at most 5) after stopping treatment. **After stopping HRT the extra risk will decrease with time, but the risk may persist for 10 years or more if you have used HRT for more than 5 years.**

{Additional information for oestrogen-only products}

~~For women who have had their womb removed and who are using oestrogen-only HRT for 5 years, little or no increase in breast cancer risk is shown.~~

Compare

Women aged 50 to ~~54~~**79** who are not taking HRT, on average, ~~9-13~~ to 17 in 1000 will be diagnosed with breast cancer over a 5-year period.

For women aged 50 who start taking oestrogen-only HRT for 5 years, there will be 16-17 cases in 1000 users (i.e. an extra 0 to 3 cases).

For women aged 50 to ~~79~~ who ~~start~~ **start** are taking oestrogen-progestogen HRT ~~over~~**for** 5 years, there will be ~~21~~ ~~13 to 23~~ cases in 1000 users (i.e. an extra 4 to ~~6~~**8** cases).

Women aged 50 to 59 who are not taking HRT, on average, 27 in 1000 will be diagnosed with breast cancer over a 10-year period.

For women aged 50 who start taking oestrogen-only HRT for 10 years, there will be 34 cases in 1000 users (i.e. an extra 7 cases)

For women aged 50 who start taking oestrogen-progestogen HRT for 10 years, there will be 48 cases in 1000 users (i.e. an extra 21 cases).

4. Possible side effects (no change proposed)

¹¹ "And" was put in strike-through font on 3 August 2020 as it needs to be deleted from the product information.

The following diseases are reported more often in women using HRT compared to women not using HRT:

- breast cancer;

Proposed amendments in SmPC and PL of HRT-products which are vaginally applied estrogens of which the systemic exposure remains within postmenopausal range

Core SmPC for HRT Annex

4.4. Special warnings and precautions for use

*The following risks have been associated with systemic HRT and apply to a lesser extent for oestrogen products for vaginal application of which the systemic exposure to the oestrogen 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 oestrogens. It is unknown if low dose vaginal oestrogens stimulate recurrence of breast cancer. The overall evidence suggests an increased risk of breast cancer in women taking combined oestrogen-progestagen and possibly also oestrogen-only systemic HRT, that is dependent on the duration of taking HRT.

The excess risk becomes apparent within a few years of use but returns to baseline within a few (at most five) years after stopping treatment.

4.8. Undesirable effects

Class effects associated with systemic HRT

The following risks have been associated with systemic HRT and apply to a lesser extent for oestrogen products for vaginal application of which the systemic exposure to estrogen remains within the normal postmenopausal range.

Breast cancer risk

- An up to 2 fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestagen therapy for more than 5 years.
- Any increased risk in users of oestrogen-only therapy is substantially lower than that seen in users of oestrogen-progestagen combinations.
- The level of risk is dependent on the duration of use (see section 4.4).
- Results of the largest randomised placebo-controlled trial (WHI study) and 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 1000 never-users of HRT over a 5-year period* ^[1]	Risk ratio & 95%CI#	Additional cases per 1000 HRT users over 5 years (95%CI)
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^[1] *Taken from baseline incidence rates in developed countries

		Gestrogen-only HRT	
50-65	9-12	1.2	1.2 (0.3)

#Overall risk ratio. The risk ratio is not constant but will increase with increasing duration on use
 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 (yrs)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95%CI	Additional cases per 1000 HRT users over 5 years (95%CI)
CEE oestrogen-only			
50-79	21	0.8 (0.7-1.0)	-4 (-6-0)* ^[2]

Core PL for HRT Annex

2. What you need to know before you use <X>

Do not take X

- If you have or have ever had **breast cancer**, or if you are suspected of having it;

HRT and cancer

The following risks apply to **hormone replacement therapy (HRT)** medicines which circulate in the blood. However <X> is for local treatment in the vagina and the absorption into the blood is very low. It is less likely that the conditions mentioned below will get worse or come back during treatment with <X>, but you should see your doctor if you are concerned.

Breast cancer

Evidence suggests that taking using <X> combined oestrogen-progestogen and possibly also oestrogen-only HRT **does not** increase the risk of breast cancer **in women who had no breast cancer in the past. It is not known if <X> can be safely used in women who had breast cancer in the past.** The extra risk depends on how long you take HRT. The additional risk becomes clear within a few years. However, it returns to normal within a few years (at most 5) after stopping treatment.

4. Possible side effects

The following diseases are reported more often in women using HRT medicines which circulate in the blood compared to women not using HRT. These risks apply less to vaginally administered treatments such as <X>:

- breast cancer;

Proposed amendments in SmPC and PL of Duavive (conjugated oestrogens/bazedoxifene)

SmPC

4.4. Special warnings and precautions for use

Breast cancer

The overall evidence ~~suggests~~ **shows an** possible increased risk of breast cancer in women taking oestrogen-only therapy **HRT** that is dependent on the duration of therapy **taking HRT**.

^[2] *WHI study in women with no uterus, which did not show an increase in risk of breast cancer

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

Observational studies have mostly reported a small increase in risk of having breast cancer **in estrogen only users** diagnosed that is ~~substantially~~¹² lower than that found in users of oestrogen-progestagen combinations (see section 4.8).

~~The excess risk becomes apparent within a few years of use but returns to baseline within a few (at most five) 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.**

The effect of CE/BZA on the risk of breast cancer is unknown.

4.8. Undesirable effects

Breast cancer risk

Breast cancer risk associated with the use of oestrogens alone is represented by several studies. ~~Any~~ **The** increased risk to users of oestrogen-only therapy is ~~substantially~~ lower than that seen in users of oestrogen-progestagen combinations. The level of risk is dependent on duration of use (see section 4.4). **Absolute risk estimations based on the r**Results of the largest randomised placebo-controlled trial (WHI-study) and **the** largest **meta-analysis of prospective** epidemiological studies ~~iesy~~ (MWS) are presented.

US WHI Oestrogen only (ET) arm - additional risk of breast cancer after 5 years’ use

Age range (yrs)	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 oestrogen-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

~~Million Women~~ **Largest meta-analysis of prospective epidemiological studies study** (Estradiol only arm) –

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

Age at start HRT range (years)	Additional cases Incidence per 1,000 never-users of HRT over a 5 year period (50-54 years)*	Risk ratio#	Additional cases per 1,000 HRT ET -users over after 5 years (95%CI)
Estradiol only Oestrogen only			
50-65	9-12 13.3	1.2	1-2 (0-3) 2.7

*Taken from baseline incidence rates in developed countries **in England in 2015 in women with BMI 27**

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

Overall risk ratio. The risk ratio is not constant but will increase with increasing duration on use.

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

Age at	Incidence per	Risk	Additional cases per 1000 HRT users after 10 years
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¹² “Substantially” was missing in the document initially published on 23 June 2020.

start HRT (years)	1000 never-users of HRT over a 10 year period (50-59 years)*	ratio	
			Oestrogen only
50	26.6	1.3	7.1

***Taken from baseline incidence rates in England in 2015 in women with BMI 27**

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

PL

2. What you need to know before you take DUAVIVE

Do not take DUAVIVE

- If you have or have ever had breast cancer, or if you are suspected of having it.

DUAVIVE and cancer

Breast cancer

Evidence ~~suggests~~ **shows** that taking oestrogen-only **hormone replacement therapy (HRT)** possibly increases the risk of breast cancer. The extra risk depends on how long you ~~take~~ **use** HRT. The additional risk becomes clear within a few ~~3~~ **3** years **of use**. However, it returns to normal within a few years (at most 5) after stopping treatment. **After stopping HRT the extra risk will decrease with time, but the risk may persist for 10 years or more if you have used HRT for more than 5 years.** For women who are using oestrogen-only HRT for 5 years, little or no increase in breast cancer risk is shown.

The effect of DUAVIVE on the risk of breast cancer is unknown.

Proposed amendments in SmPC and PL of tibolone¹³

SmPC

4.4. 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 (see also below and section 4.8).

Breast cancer

Evidence with respect to breast cancer risk in association with tibolone is inconclusive. **A meta-analysis of epidemiological studies, including t**~~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, see section 4.8. These results could not be confirmed in a study using the General Practice Research Database (GPRD). 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.

¹³ The translations of the product information changes for tibolone will be published on 6 July 2020.

4.8. Undesirable effects

Breast cancer risk

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestogen therapy for more than 5 years.
- ~~The~~ **Any** increased risk in users of oestrogen-only and tibolone therapy is lower than seen in users of oestrogen-progestogen combinations.
- The level of risk is dependent on the duration of use (see section 4.4).
- 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 1000 never-users of HRT over a 5 year period*	Risk & 95%CI#	Additional cases per 1000 HRT users over 5 years (95%CI)
Oestrogen only HRT			
50-65	9-12	1.2	1-2 (0-3)
Combined oestrogen-progestagen			
50-65	9-12	1.7	6 (5-7)
Tibolone			
50-65	9-12	1.3	3 (0-6)
*With reference to the baseline incidence in developed countries			
#Overall risk ratio. The risk ratio is not constant but will increase with increasing duration of use			

PL

2. What you need to know before you use <X>

Do not take X

- if you have or have ever had **breast cancer**, or if you are suspected of having it;

Breast cancer

Evidence suggests **shows** that taking ~~combined oestrogen-progestogen and possibly also oestrogen-only~~ **tibolone** increases the risk of breast cancer. The extra risk depends on how long you ~~take~~**use** HRT **tibolone**. The additional risk becomes clear within a few years of use. **In studies with HRT, after stopping HRT the extra risk decreased with time, but the risk may persist for 10 years or more when women have used HRT for more than 5 years.** However, the risk decreases after stopping treatment and it returns to normal within a few years (at most 5). **No data for persistence of risk after stopping are available for tibolone, but a similar pattern cannot be ruled out.**

Compare

Women taking <X> have a lower risk than women using combined HRT and a comparable risk with oestrogen-only HRT.

4. Possible side effects (no change proposed)

The following diseases are reported more often in women using HRT compared to women not using HRT:

- breast cancer

1.4. Mirtazapine – Amnesia

Authorisation procedure	Non-centralised
EPITT No	19506
PRAC rapporteur(s)	Liana Gross-Martirosyan (NL)
Date of adoption	14 May 2020

Recommendation

Based on the available data, the PRAC concluded that there is a causal association between the risk of amnesia and the use of mirtazapine containing products.

Therefore, the MAH(s) of mirtazapine-containing medicinal product(s) should submit a variation within 2 months, to amend the product information as described below (new text to be added underlined):

Summary of product characteristics

4.8. Undesirable effects

Table of ADRs - Nervous system disorders

Frequency 'common': Amnesia*

*In most cases patients recovered after drug withdrawal.

Package leaflet

4. Possible side effects

Frequency 'common': Memory problems, which in most cases resolved when treatment was stopped.

1.5. Mirtazapine – Drug reaction with eosinophilia and systemic symptoms (DRESS)

Authorisation procedure	Non-centralised
EPITT No	19565
PRAC rapporteur(s)	Liana Gross-Martirosyan (NL)
Date of adoption	14 May 2020

Recommendation

Based on the available data, the PRAC concluded that there is a causal association between the risk of drug reaction with eosinophilia and systemic symptoms (DRESS) and the use of mirtazapine containing products.

Therefore, the MAH(s) of mirtazapine-containing medicinal product(s) should submit a variation within 2 months, to amend the product information as described below (new text to be added underlined):

Summary of product characteristics

4.4. Special warnings and precautions for use

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), bullous dermatitis and erythema multiforme, which can be life-threatening or fatal, have been reported in association with <mirtazapine> treatment.

If signs and symptoms suggestive of these reactions appear, <mirtazapine> should be withdrawn immediately.

If the patient has developed one of these reactions with the use of <mirtazapine>, treatment with <mirtazapine> must not be restarted in this patient at any time.

4.8. Undesirable effects

Summary of safety profile

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), bullous dermatitis and erythema multiforme have been reported in association with <mirtazapine> treatment (see section 4.4).

Table of ADRs - Skin and subcutaneous tissue disorders

Drug reaction with eosinophilia and systemic symptoms (DRESS)

Frequency: not known

Package leaflet

2. What you need to know before you use <mirtazapine>

DO NOT TAKE - OR - TELL YOUR DOCTOR BEFORE TAKING <mirtazapine>:

If you have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after taking <mirtazapine> or other medicinal product(s).

Take special care with <mirtazapine>:

Serious skin reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported with the use of <mirtazapine>. Stop using and seek medical attention immediately if you notice any of the symptoms described in section 4 in relation to these serious skin reactions.

If you have ever developed any severe skin reactions, treatment with <mirtazapine> should not be restarted.

4. Possible side effects

Stop using mirtazapine and contact your doctor or seek medical attention immediately if you develop one of the following serious side effects:

Frequency not known:

- Reddish patches on the trunk which are target-like macules or circular, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (Stevens-Johnson syndrome, toxic epidermal necrolysis).
- Widespread rash, high body temperature and enlarged lymph nodes (DRESS syndrome or drug hypersensitivity syndrome).

1.6. Sertraline – Microscopic colitis

Authorisation procedure	Non-centralised
EPITT No	19513
PRAC rapporteur(s)	Liana Gross-Martirosyan (NL)
Date of adoption	14 May 2020

Recommendation

Having considered the available evidence in EudraVigilance and in the literature, the PRAC has agreed that the Marketing Authorisation Holders (MAHs) of sertraline-containing medicinal products should submit a variation within 2 months, to amend the product information as described below (new text underlined):

Summary of product characteristics

4.8. Undesirable effects

Gastrointestinal disorders

Frequency “not known”: Colitis microscopic

Package leaflet

4. Possible side effects

Not known: frequency cannot be estimated from the available data

Inflammation of the colon (causing diarrhoea)

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Olaparib	Angioedema (19558)	Amelia Cupelli (IT)	Assess within the ongoing PSUR procedure (submission by 10 June 2020 with the comments to the preliminary PSUR assessment report)	AstraZeneca AB
Pembrolizumab	Sjögren's syndrome (19564)	Menno van der Elst (NL)	Supplementary information requested (submission by 29 July 2020)	Merck Sharp & Dohme B.V.

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Andexanet alfa	Erroneous assay results for levels of anti-factor Xa activity (19493)	Menno van der Elst (NL)	Distribute a Direct Healthcare Professional Communication (DHPC) according to the text and communication plan agreed with the CHMP	Portola Netherlands B.V.
Dabrafenib; trametinib	Disseminated intravascular coagulation (DIC) (19510)	Annika Folin (SE)	Routine pharmacovigilance	Novartis Europharm Limited
Dipeptidyl peptidase-4 (DPP4) inhibitors: 1. Vildagliptin; vildagliptin, metformin hydrochloride	Rhabdomyolysis (19466)	Menno van der Elst (NL)	1. Continue monitoring in the next PSUSA (202102) by including "rhabdomyolysis" as a part of the important potential risk "Muscle events/myopathy with and without concurrent statin use".	1. MAHs of vildagliptin-containing products

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
2. All other DPP4 inhibitors ¹⁴			2. Continue monitoring in the next PSURs	2. MAHs of all other DPP4 inhibitors
Fluoroquinolones for systemic and inhalation formulations: ciprofloxacin; delafloxacin; levofloxacin; lomefloxacin; moxifloxacin; norfloxacin; ofloxacin; pefloxacin; prulifloxacin; rufloxacin	Heart valve regurgitation, cervical artery dissection, and aortic aneurysm and dissection (19522)	Martin Huber (DE)	· Provide comments on the proposed product information update and Direct Healthcare Professional Communication (DHPC) (submission by 5 June 2020)	· Bayer; Sanofi, Neuraxpharm, Meda Pharma, Sandoz, Angelini, Lanova Farmaceutici, A. Menarini, Horizon Pharma Europe
			· Verify whether specified cases have been entered in EudraVigilance	· Bayer, Sanofi
			· Monitor in PSURs disorders of arteries other than the aorta	· MAHs of fluoroquinolones for systemic and inhalation formulations

¹⁴ Alogliptin; alogliptin, metformin hydrochloride; alogliptin, pioglitazone; linagliptin; saxagliptin; saxagliptin, dapagliflozin; saxagliptin, metformin hydrochloride; sitagliptin; sitagliptin, ertugliflozin; sitagliptin, metformin