22 June 2020[1]
EMA/PRAC/257439/2020
Pharmacovigilance Risk Assessment Committee (PRAC)

New product information wording – Extracts from PRAC recommendations on signals

Adopted at the 11-14 May 2020 PRAC

The product information wording in this document is extracted from the document entitled 'PRAC recommendations on signals' which contains the whole text of the PRAC recommendations for product information update, as well as some general guidance on the handling of signals. It can be found ***here*** (in English only).

New text to be added to the product information is underlined. Current text to be deleted is ~~struck through~~.

1. Baricitinib – Diverticulitis (EPITT no 19496)

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

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

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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.

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)

2. Buprenorphine; buprenorphine, naloxone – Drug-drug interaction with serotonergic drugs leading to serotonin syndrome (EPITT no 19475)

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.

3. Hormone replacement therapy (HRT)[2] – New information on the known risk of breast cancer (EPITT no 19482)

New text in **bold underlined**.

Proposed amendments in core summary of product characteristics (SmPC) and package leaflet (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).

[…]

~~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.**

[…]

4.8. Undesirable effects

Breast cancer risk

- […]
- **The** ~~Any~~ increased risk in users of oestrogen-only therapy is ~~substantially~~ lower than that seen in user of oestrogen-progestagen combinations.
- […]
- **Absolute risk estimations based on** ~~The R~~**r**esults of the largest randomised placebo-controlled trial (WHI-study) and **the** largest **meta-analysis of prospective** epidemiological stud~~y~~**ies** ~~(MWS)~~ are presented.

~~Million Women~~ **Largest meta-analysis of prospective epidemiological** stud**iesy –**

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

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

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.

Core PL for HRT products

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

[…]

Breast cancer

Evidence ~~suggests~~ **shows** that taking combined oestrogen-progestogen and ~~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** ~~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).

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

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

~~**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)~~
		~~**Oestrogen only HRT**~~	
~~50-65~~	~~9-12~~	~~1.2~~	~~1-2 (0-3)~~

~~*[1] *Taken from baseline incidence rates in developed countries*~~

~~#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 >

[…]

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~~s~~ 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** a**n** ~~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*~~

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 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.**

[…]

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**~~R~~esults of the largest randomised placebo-controlled trial (WHI-study) and **the** largest **meta-analysis of prospective** epidemiological stud**ies**~~y~~ ~~(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) -~~

E~~e~~stimated 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 start HRT (years)	**Incidence per 1000 never-users of HRT over a 10 year**	**Risk ratio**	**Additional cases per 1000 HRT users after 10 years**

	period (50-59 years)*		
		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

[…]

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** 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.~~

[…]

Proposed amendments in SmPC and PL of tibolone

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

4. Mirtazapine – Amnesia (EPITT no 19506)

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.

5. Mirtazapine – Drug reaction with eosinophilia and systemic symptoms (DRESS) (EPITT no 19565)

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).

6. 6. Sertraline – Microscopic colitis (EPITT no 19513)

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)