



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

17 December 2015  
EMA/PRAC/788914/2015  
Pharmacovigilance Risk Assessment Committee (PRAC)

## PRAC recommendations on signals

Adopted at the PRAC meeting of 30 November - 3 December 2015

This document provides an overview of the recommendations adopted by the Pharmacovigilance Risk Assessment Committee (PRAC) on the signals discussed during the meeting of 30 November - 3 December 2015 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT]<sup>1</sup> 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 (14-17 December 2015) 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.

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.

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<sup>1</sup> The relevant EPITT reference number should be used in any communication related to a signal.



**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 information<sup>2</sup>

## **1.1. Hormone replacement therapy (HRT) medicinal products, which are not pharmaceutical forms for vaginal use, containing oestrogens or combined oestrogens-progestagens (tibolone containing products also concerned); bazedoxifene, oestrogens conjugated – Increased risk of ovarian cancer**

|                                |                                 |
|--------------------------------|---------------------------------|
| <b>Authorisation procedure</b> | Centralised and non-centralised |
| <b>EPITT No</b>                | 18258                           |
| <b>PRAC rapporteur(s)</b>      | Menno van der Elst (NL)         |
| <b>Date of adoption</b>        | 3 December 2015                 |

### **Recommendation**

PRAC has considered the comments received following the consultation on the update of the product information for Hormone Replacement Therapy (HRT) products.

PRAC is of the opinion that the results of the meta-analysis published in the Lancet<sup>3</sup> on the risk of ovarian cancer associated with the use of HRT products provide strong evidence to justify a revision of the product information.

The following modifications of the Summary of Product Characteristics (SPC) and Package Leaflet for post-menopausal HRT products have been endorsed by PRAC (new text underlined, deleted text ~~strike through~~). They should be implemented within 3 months, following the publication of the recommendation, by all marketing authorisations holders of medicinal products containing oestrogens (tibolone also concerned) or combined oestrogens-progestagens, which are not pharmaceutical forms for vaginal use.

#### **1. For oestrogen only and combined oestrogen-progestagen HRT products**

##### **Summary of product characteristics (SmPC) section 4.4: Special warnings and precautions for use**

Ovarian cancer

Ovarian cancer is much rarer than breast cancer.

~~Long term (at least 5–10 years) use of oestrogen-only HRT products has been associated with a slightly increased risk of ovarian cancer (see section 4.8).~~ Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking oestrogen-only or combined oestrogen-progestagen HRT, which becomes apparent within 5 years of use and diminishes over time after stopping.

<sup>2</sup> Translations in all official EU languages of the new product information adopted by PRAC are also available to MAHs on the EMA website.

<sup>3</sup> Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies; Collaborative Group on Epidemiological Studies of Ovarian Cancer; The Lancet, Volume 385, Issue 9980, 1835 – 1842, February, 13, 2015

Some other studies, including the WHI trial, suggest that the ~~long-term~~ use of combined HRTs may ~~confer~~ be associated with a similar, or slightly smaller risk (see Section 4.8).

#### **SmPC section 4.8: Undesirable effects**

Ovarian cancer

~~Long-term~~ Use of oestrogen-only ~~and or~~ combined oestrogen-progestagen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see Section 4.4). ~~In the Million Women Study 5 years of HRT resulted in 1 extra case per 2500 users.~~

A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using HRT compared to women who have never used HRT (RR 1.43, 95% CI 1.31-1.56). For women aged 50 to 54 years taking 5 years of HRT, this results in about 1 extra case per 2000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2000 will be diagnosed with ovarian cancer over a 5-year period.

#### **Package Leaflet**

##### **2. BEFORE YOU TAKE X**

Ovarian cancer

Ovarian cancer is rare - much rarer than breast cancer. ~~A slightly increased risk of ovarian cancer has been reported in women taking HRT for at least 5 to 10 years. The use of oestrogen-only or combined oestrogen-progestagen HRT has been associated with a slightly increased risk of ovarian cancer.~~

The risk of ovarian cancer varies with age. For example, in ~~W~~women aged 50 to ~~5469~~ who are not taking HRT, ~~on average~~ about 2 women in ~~24000~~ will be diagnosed with ovarian cancer over a 5-year period. For women who have been taking HRT for 5 years, there will be ~~between 2 and about~~ 3 cases per ~~24000~~ users (i.e. ~~up to about~~ 1 extra case).

##### **2. For tibolone containing products**

#### **SmPC section 4.4: Special warnings and precautions for use**

Ovarian cancer

Ovarian cancer is much rarer than breast cancer.

~~Long-term (at least 5-10 years) use of oestrogen-only HRT products has been associated with a slightly increased risk of ovarian cancer (see section 4.8). Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking oestrogen-only or combined oestrogen-progestagen HRT, which becomes apparent within 5 years of use and diminishes over time after stopping.~~

Some other studies, including the Women's Health Initiative (WHI) trial, suggest that the ~~long-term~~ use of combined HRTs may ~~confer~~ be associated with a similar, or slightly smaller risk (see Section 4.8).

In the Million Women Study, it was shown that the relative risk for ovarian cancer with use of tibolone was similar to the risk associated with use of other types of HRT.

#### **SmPC section 4.8: Undesirable effects**

Other adverse reactions have been reported in association with oestrogen and oestrogen-progestogen treatment:

##### Ovarian cancer

~~Long term use~~ Use of estrogen-only ~~and~~ or combined estrogen-progestogen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see Section 4.4).

A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using HRT compared to women who have never used HRT (RR 1.43, 95% CI 1.31-1.56). For women aged 50 to 54 years taking 5 years of HRT, this results in about 1 extra case per 2000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2000 will be diagnosed with ovarian cancer over a 5-year period.

In the Million Women Study, taking 5 years of HRT tibolone resulted in 1 extra case per 2500 users (see Section 4.4). ~~This study showed that the relative risk for ovarian cancer with tibolone was similar to the risk with other types of HRT.~~

#### **Package Leaflet**

##### **2. BEFORE YOU TAKE X**

##### Ovarian cancer

Ovarian cancer is rare - much rarer than breast cancer. The use of oestrogen-only or combined oestrogen-progestagen HRT has been associated with a slightly increased risk of ovarian cancer.

~~The risk of ovarian cancer varies with age. For example, in A slightly increased risk of ovarian cancer has been reported in women taking HRT for at least 5 to 10 years. Compare~~ For women aged 50 to ~~54~~69 who are not taking HRT, ~~on average~~ about 2 women in ~~2~~4000 will be diagnosed with ovarian cancer over a 5-year period. For women who have been taking HRT for 5 years, there will be ~~between 2 and~~ about 3 cases per ~~2~~4000 users (i.e. ~~up to~~ about 1 extra case).

With use of X, the increased risk of ovarian cancer is similar to other types of HRT.

##### **3. For DUAVIVE product**

#### **SmPC section 4.4: Special warnings and precautions for use**

##### Ovarian cancer

Ovarian cancer is much rarer than breast cancer.

~~Long term (at least 5-10 years) use of oestrogen-only HRT products has been associated with a slightly increased risk of ovarian cancer (see section 4.8).~~ Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking oestrogen-only HRT, which becomes apparent within 5 years of use and diminishes over time after stopping.

Some other studies, including the WHI trial, suggest that use of combined HRTs may be associated with a similar or slightly smaller risk (see Section 4.8).

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

## SmPC section 4.8: Undesirable effects

Ovarian cancer

~~Long-term use~~ Use of oestrogen-only HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see Section 4.4).

A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using HRT compared to women who have never used HRT (RR 1.43, 95% CI 1.31-1.56). In the Million Women Study For women aged 50 to 54 years taking 5 years of HRT, this result seen in about 1 extra case per 2,500 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2000 will be diagnosed with ovarian cancer over a 5-year period.

### Package Leaflet

#### 2. BEFORE YOU TAKE DUVAVIVE

Ovarian cancer

Ovarian cancer is rare - much rarer than breast cancer. The use of oestrogen-only HRT has been associated with a slightly increased risk of ovarian cancer.

~~A slightly increased risk of ovarian cancer has been reported in women taking HRT for at least 5 to 10 years.~~

The risk of ovarian cancer varies with age. For example, in women aged 50 to 54~~69~~ who are not taking HRT, on average about 2 women in 24,000 will be diagnosed with ovarian cancer over a 5-year period. For women who have been taking HRT for 5 years, there will be ~~between 2 and~~ about 3 cases per 24,000 users (i.e. about up to 1 extra case). Talk to your doctor if you have any concerns.

The effect of DUAIVIVE on the risk of ovarian cancer is unknown.

## 1.2. Human fibrinogen, human thrombin – Intestinal obstruction

|                         |                                   |
|-------------------------|-----------------------------------|
| Authorisation procedure | Centralised                       |
| EPITT No                | 18373                             |
| PRAC rapporteur(s)      | Brigitte Keller-Stanislawski (DE) |
| Date of adoption        | 3 December 2015                   |

### Recommendation

Having considered the available evidence from EudraVigilance, the literature, the data submitted by the MAH and the proposal for an update of the product information, the PRAC recommended that the MAH of TachoSil (Takeda Austria GmbH) should submit within 30 days a variation to update the product information as follows:

## SmPC

### 4.4 Special warnings and precautions for use

To prevent the development of tissue adhesions at undesired sites, ensure tissue areas outside the desired application area are adequately cleansed before administration of TachoSil (see section 6.6). Events of adhesions to gastrointestinal tissues leading to gastrointestinal obstruction have been reported with use in abdominal surgery carried out in proximity to the bowel.

### 4.8 Undesirable effects

Gastrointestinal disorders:

Frequency 'unknown': Intestinal obstruction (in abdominal surgeries)

General disorders and administration site conditions:

Frequency 'unknown': Adhesions

### 6.6 Special precautions for disposal and other handling

Pressure is applied with moistened gloves or a moist pad. Due to the strong affinity of collagen to blood, TachoSil may also stick to surgical instruments, ~~or~~ gloves or adjacent tissues covered with blood. This can be avoided by cleansing surgical instruments, and gloves and adjacent tissues before application. It is important to note that failure to adequately clean adjacent tissues may cause adhesions (see section 4.4). After pressing TachoSil to the wound, the glove or the pad must be removed carefully. To avoid TachoSil from being pulled loose it may be held in place at one end, e.g. with a pair of forceps.

## Package leaflet

### 2. What you need to know before TachoSil is used

#### Warnings and precautions

After abdominal surgery and if TachoSil sticks to nearby tissues, it is possible that scar tissues can develop in the operated area. Scar tissues can cause surfaces in your bowel to stick together, which can lead to blockage of the bowel.

#### 4. Possible side effects

Scar tissues may develop in some patients after surgery and use of TachoSil. Bowel obstruction and pain following abdominal surgeries can also occur. The frequency of these types of events is not known (cannot be estimated from available data). Your surgeon will make sure to clean the operating area when applying TachoSil to reduce this risk.

## Instructions for Use

3. Cleanse surgical instruments, ~~or~~ gloves and adjacent tissues, if necessary. TachoSil may stick to surgical instruments, or gloves or adjacent tissues covered with blood. It is important to note that failure to adequately clean adjacent tissues may cause adhesions.

The MAH should distribute a DHPC letter according to the agreed communication plan to raise awareness among concerned health care professionals in the EU, including the surgeons, and to promote reporting of any suspected adverse reactions.

An updated Risk Management Plan of TachoSil should be submitted within this variation to include gastrointestinal obstruction as an important identified risk.

## 2. Recommendations for submission of supplementary information

| INN        | Signal (EPITT No)   | PRAC<br>Rapporteur          | Action for MAH   | MAH                                     |
|------------|---|-----------------------------|--|---|
| Adalimumab | Glomerulonephritis (18528)  | Ulla Wändel<br>Liminga (SE) | Supplementary information requested (submission by 10/02/2016) | AbbVie Ltd                              |
| Dabigatran | Pulmonary alveolar haemorrhage (18516)                                | Torbjörn Callreus (DK)      | Assess in the next PSUR (submission by 27/05/2016)             | Boehringer Ingelheim International GmbH |
| Infliximab | Thyroid gland disorders (18530)                                       | Ulla Wändel<br>Liminga (SE) | Supplementary information requested (submission by 10/02/2016) | Janssen Biologics B.V.                  |
| Olanzapine | Drug reaction with eosinophilia and systemic symptoms (DRESS) (18534) | Jaakkola Kimmo (FI)         | Supplementary information requested (submission by 10/02/2016) | Eli Lilly Nederland B.V.                |
| Vismodegib | Angioedema (18526)  | Ulla Wändel<br>Liminga (SE) | Supplementary information requested (submission by 10/02/2016) | Roche Registration Ltd                  |



### 3. Other recommendations

| INN                            | Signal (EPITT No)   | PRAC<br>Rapporteur             | Action for MAH          | MAH            |
|--------------------------------|---|--------------------------------|-------------------------|----------------|
| Flucloxacillin;<br>paracetamol | Metabolic acidosis<br>following administration<br>of flucloxacillin in<br>association with<br>paracetamol (18514) | Margarida<br>Guimarães<br>(PT) | No action at this stage | Not applicable |