



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 December 2015
EMA/PRAC/711684/2015
Pharmacovigilance Risk Assessment Committee (PRAC)

New product information wording – Extracts from PRAC recommendations on signals

Adopted at the 30 November – 3 December 2015 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. 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); DUAVIVE (bazedoxifene, oestrogens conjugated) – Increased risk of ovarian cancer (EPITT no 18258)

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.~~



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 women aged 50 to 54 who are not taking HRT, on average about 2 women in 2000 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 2000 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.

2. TACHOSIL (Human fibrinogen, human thrombin) – Intestinal obstruction (EPITT no 18373)

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.