6 July 2020[1]
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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC recommendations on signals

Adopted at the 8-11 June 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 8-11 June 2020 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT][2] 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 (22-25 June 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.

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.

[1] Expected publication date. The actual publication date can be checked on the webpage dedicated to PRAC recommendations on safety signals.
[2] The relevant EPITT reference number should be used in any communication related to a signal.

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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[3]

1.1. Desogestrel – Suppressed lactation

Authorisation procedure	Non-centralised
EPITT No	19504
PRAC rapporteur(s)	Annika Folin
Date of adoption	11 June 2020

Recommendation

Having reviewed the cumulative review provided by the MAH of Cerazette, including the available data from clinical trials, literature and EudraVigilance, the PRAC has agreed that while a causal relationship between desogestrel and suppressed lactation cannot be completely established, the current SmPCs and Patient Leaflets are too conclusive and do not reflect the current data. Therefore, the MAHs of desogestrel-containing progestogen only pills (POPs), 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

4.6. Fertility, pregnancy and lactation

Breastfeeding

Based on clinical study data, <product name> does not appear to influence the production or the quality (protein, lactose, or fat concentrations) of breast milk. However, there have been infrequent postmarketing reports of a decrease in breast milk production while using <product name>. ~~s~~Small amounts of etonogestrel are excreted in the breast milk. As a result, 0.01 - 0.05 microgram etonogestrel per kg body weight per day may be ingested by the child (based on an estimated milk ingestion of 150 ml/kg/day). Like other progestogen-only pills, <product name> can be used during breast feeding.

Limited long-term follow-up data are available on children, whose mothers started using <product name> during the 4th to 8th week post-partum. They were breast-fed for 7 months and followed up to 1.5 years (n=32) or to 2.5 years (n=14) of age. Evaluation of growth and physical and psychomotor development did not indicate any differences in comparison to nursing infants, whose mother used a copper-IUD. Based on the available data <product name> may be used during lactation. The development and growth of a nursing infant, whose mother uses <product name>, should, however, be carefully observed.

Section 5 – Pharmacological properties

5.1 Pharmacodynamic properties

Mechanism of action

<Product name> is a progestogen-only pill, which contains the progestogen desogestrel. Like other progestogen-only pills, <product name> ~~is best suited for use during breast feeding and~~ can be used for women who may not or do not want to use oestrogens. In contrast to traditional progestogen-only

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

pills, the contraceptive effect of <product name> is achieved primarily by inhibition of ovulation. Other effects include increased viscosity of the cervical mucus.

[…]

Package leaflet

Breast-feeding

<Product name> may be used while you are breast-feeding. <Product name> does not appear to influence the production or the quality of breast milk. However, there have been infrequent reports of a decrease in breast milk production while using <product name>. A~~a~~ small amount of the active substance of <product name> passes over into the milk.

1.2. Hormone replacement therapy (HRT): tibolone – New information on the known risk of breast cancer

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

Tibolone was discussed at the 14-17 May 2020 PRAC meeting as part of the signal on hormone replacement therapy. The translations of the tibolone product information changes are published with the translations of the 8-11 June 2020 PRAC recommendations on signals.

Proposed amendments in SmPC and PL of tibolone

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**~~T~~he 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.

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# ratio**	**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

1.3. Macrogol-containing products (all molecular weights and combinations) for bowel preparation – Colitis ischaemic

Authorisation procedure	Non-centralised
EPITT No	19517
PRAC rapporteur(s)	Ilaria Baldelli (IT)
Date of adoption	11 June 2020

Recommendation

Having considered the available evidence from case reports in EudraVigilance and in the literature and also taking into account the seriousness of the event, the PRAC has agreed that MAHs of macrogol containing products (all molecular weights and combinations) authorised for the bowel preparation 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

Ischaemic colitis

Post-marketing cases of ischaemic colitis, including serious, have been reported in patients treated with macrogol for bowel preparation. Macrogol should be used with caution in patients with known risk factors for ischaemic colitis or in case of concomitant use of stimulant laxatives (such as bisacodyl or sodium picosulfate). Patients presenting with sudden abdominal pain, rectal bleeding or other symptoms of ischaemic colitis should be evaluated promptly.

Package leaflet

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

Warnings and precautions

[…]

- If you experience sudden abdominal pain or rectal bleeding when taking <product name> for bowel preparation, contact your doctor or seek medical advice immediately.

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Capecitabine	Anaphylactic reaction (19561)	Martin Huber (DE)	Supplementary information requested (submission by 23 September 2020)	Roche Registration GmbH
Cefepime	Drug reaction with eosinophilia and systemic symptoms (DRESS) (17866)	Ana Sofia Martins (PT)	Supplementary information requested (submission by 26 August 2020)	Bristol-Myers Squibb
Chloroquine; hydroxychloroquine	Psychiatric disorders (19572)	Anette Kirstine Stark (DK)	Supplementary information requested (submission by 13 July 2020)	MAHs for the innovators of chloroquine and hydroxychloroquine containing products
Cladribine	Seizure (19573)	Márcia Silva (PT)	Assess in the next PSUR (submission by 15 September 2020)	Merck Europe B.V.
Immune checkpoint inhibitors: atezolizumab; avelumab; cemiplimab; durvalumab; ipilimumab; nivolumab; pembrolizumab	Eosinophilic fasciitis (19567)	Brigitte Keller-Stanislawski (DE)	Supplementary information requested (submission by 26 August 2020)	Merck Sharp & Dohme B.V., Bristol-Myers Squibb Pharma EEIG, Roche Registration GmbH, Merck Europe B.V., AstraZeneca AB, Regeneron Ireland U.C.

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Amitriptyline; bupropion (incl. its combination with naltrexone); citalopram; desvenlafaxine; duloxetine; escitalopram; fluoxetine; fluvoxamine; milnacipran; mirtazapine; paroxetine; sertraline; trazodone; venlafaxine; vortioxetine	Postpartum haemorrhage (19552)	Ulla Wändel Liminga (SE)	· No update of the product information warranted	· MAHs of mirtazapine, trazodone, amitriptyline and bupropion (incl. its combination with naltrexone) containing products
			· No action (wording already agreed remains adequate)	· MAHs of duloxetine containing products
			· Monitor haemorrhage and postpartum haemorrhage events in the next PSUSA procedure	· Lundbeck (innovator MAH of amitriptyline)
			· Provide comments to the proposed updates to the product information (submission by 29 July 2020)	· Innovator MAHs of citalopram (Lundbeck), desvenlafaxine (Pfizer), escitalopram (Lundbeck), fluoxetine (Lilly), fluvoxamine (Mylan), milnacipran (Pierre Fabre), paroxetine (GSK), sertraline (Pfizer), venlafaxine (Pfizer), vortioxetine (Lundbeck)