NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
E-mail: ReferralNotifications@ema.europa.eu

This notification is a referral under Article 31 of Directive 2001/83/EC to the PRAC made by France - ANSM:

Product Name(s) in the Referring Member State, if applicable	PROGESTERONE RETARD PHARLON 500 mg/2 ml, solution injectable IM en ampoule
Active substance(s)	Hydroxyprogesterone
Pharmaceutical form(s)	All
Strength(s)	All
Route(s) of Administration	All
Marketing Authorisation Holder(s) in the referring Member State	Bayer

Background

Hydroxyprogesterone caproate (17-OHPC) is a synthetic ester of 17-OH progesterone (17-OHP), an endogenous progestogen with an affinity for progesterone receptors. Physiologically, progesterone is transformed into 17-OHP, which is an intermediate in the biosynthesis of steroids (androgens, oestrogens, cortisol/corticosteroids and aldosterone). 17-OHP has luteomimetic and gestagen properties of progesterone secreted by the ovarian *corpus luteum*.

17-OHPC is an ester, not cleaved and thus it is neither converted into 17-OHP nor progesterone. 17-OHPC is excreted unchanged or under conjugated metabolites.

In vitro, the binding affinity of 17-OHPC to progesterone receptors seems either similar or weaker than endogenous progesterone[1,2]. *In vitro* and preclinical studies showed that 17-OHPC effects on the myometrium and cervix differ from those observed with progesterone[2],

meaning that these two substances, despite their similarities, have different pharmacological profiles.
Hydroxyprogesterone-containing products (caproate) are authorised in three countries in the European Union, namely France, Italy and Austria.
In France, the approved indications are:

- Gynecological indications when the parenteral route is essential:
  - Disorders related to progesterone deficiency (dysmenorrhea, menstrual irregularities, premenstrual syndrome, mastodynia, etc),
  - Sterility due to luteal insufficiency,
  - Artificial cycle in association with an estrogen.
- Obstetrical indications:
  - Threatened abortion or prevention of repeated abortion by proven luteal insufficiency,
  - Threat of premature delivery in connection with uterine hypermotility.

In Austria, the only authorised indication is threatened abortion. In Italy, the indications are as follows: threatened abortion, habitual abortion, dysfunctional juvenile and climacteric metrorrhagia, primary and secondary amenorrhea, protection of pregnancy in the event of surgery, luteal insufficiency.

Issues to be considered:

Safety issue:
In November 2021, a pharmacoepidemiological study (Murphy et al 2022[3]) was identified in the literature and showed that *in utero* exposure to 17-OHPC may be associated with a higher risk of cancer in offspring.

This US cohort study aimed to assess the risk of adult cancer development in children of mothers who received 17-OHPC during pregnancy in the 1960s, when the indication for 17 OHPC was mainly in repeated abortions.

1,008 descendants of this cohort were diagnosed with cancer over 730,817 person-years of follow-up. Approximately 1.0% of children (n=234) were exposed *in utero* to 17-OHPC.
In total, the adjusted hazard ratio (aHR) of developing cancer in offspring when exposed *in utero* to 17-OHPC is 1.99 [95% CI 1.31-3.02]. Exposure during the first trimester was associated with an increased risk of cancer in the offspring (aHR=2.57, 95% CI [1.59-4.15]), and the risk increased with the number of injections (aHR=1.80, 95% CI [1.12-2.90] for 1-2 injections, and aHR=3.07, 95% CI [1.34-7.05] for 3 or more injections). Subgroups analyses showed that exposure during the second or third trimester was associated with an increased risk for males but not for females, and that exposure during the first trimester was associated with an increased risk of colorectal, prostate and paediatric brain cancer in offspring. The mechanism that could lead to an increased risk of cancer in the offspring is not yet known. However, the authors suggest that 17-OHPC, as a synthetic ester of 17-OHP, could act as an endocrine disruptor. Indeed, the highest risk was observed when the offspring was exposed during the first pregnancy trimester, which is supportive of a potential endocrine disruptive effect of the 17-OHPC during the embryogenesis.

Despite the presence of limitations in this study, the statistically significant associations, in particular the dose-effect relationship, is of concern.

Two of the indications authorised in European Union can lead to exposure to 17-OHPC during the first trimester of pregnancy, which seems to be associated with the highest risk of cancer in the offspring: sterility due to luteal insufficiency and threatened abortion. Indeed,

elimination of 17-OHPC is slow, around 30 days after injection meaning that injection during luteal phase can lead to early embryo exposure.

Efficacy issue:
The ANSM also noted that in 2020, results of a large multicentre double-blind randomized controlled trial conducted in the US between 2009 and 2018 (Blackwell et al 2020[4]), showed that 17-OHPC has no benefit over placebo in preventing threatened preterm labour neither for the mother (no extension of the duration of pregnancy) nor for the newborn (no reduction in serious events associated with prematurity). This large clinical trial was an obligation set to the MAH (AMAG Pharmaceuticals) in the US at the time of the marketing authorisation (accelerated procedure) in 2011. Based on these results, the FDA's Center for Drug Evaluation and Research (CDER) proposed the revocation of the marketing authorisation of the hydroxyprogesterone-containing products in October 2020 on the basis of questionable benefit and a potential risk on neonates and foetus. The marketing authorisation was officially revoked in the US on the grounds of lack of benefit on 06 April 2023[5].

Status at national level (France):

Given these new safety and efficacy data, the ANSM sent a letter to the MAH (Bayer) in France in March 2022 to question the relevance of maintaining the indications of their medicinal product. At the time, the ANSM highly encouraged the MAH to submit the answers within a worksharing procedure in order to have a common evaluation with the two other EU Member States where hydroxyprogesterone-containing products are authorised. However, the MAH submitted in May 2022 a national variation in France that is currently still ongoing. In April 2023, the MAH announced the cessation of batch release to the French market for commercial reasons, but batch recall is not considered by the MAH and the expiration of the last batches is in May 2026. The national variation is currently in clock-stop and nodefinitive recommendation has been given yet.

Scope of the referral

In summary, there is a possible risk of cancer in the offspring of women treated during their pregnancy with hydroxyprogesterone, especially when the exposure is during the first trimester of pregnancy; furthermore recent efficacy data show that hydroxyprogesterone failed to prevent preterm birth. All these data warrant an in-depth review of the benefit-risk balance of all the approved therapeutic indications of hydroxyprogesterone containing products. While Bayer expressed its intention to discontinue marketing of its product, this will still allow for a potential exposure of women to hydroxyprogesterone up to 2026 in France and possibly beyond in Austria and Italy.

In view of the above and the necessity to take an action at EU level, France considers that it is in the interest of the Union to refer the matter to the PRAC and requests that it gives its recommendation under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these medicinal products should be maintained, varied, suspended, or revoked.

As the request results from the evaluation of data resulting from pharmacovigilance activities, the opinion should be adopted by the CMDh on the basis of a recommendation of the PRAC.

Signed CHRISTELLE RATIGNIER CARBONNEIL ID Signature numérique de CHRISTELLE RATIGNIER CARBONNEIL ID Date : 2023.05.05 13:50:13 +02'00' Date

References:

1. Attardi, B. J. *et al.* Comparison of progesterone and glucocorticoid receptor binding and stimulation of gene expression by progesterone, 17-alpha hydroxyprogesterone caproate (17-OHPC), and related progestins. *Am. J. Obstet. Gynecol.* 197, 599.e1-599.e7 (2007).
2. Romero, R. & Stanczyk, F. Z. Progesterone is not the same as 17α-hydroxyprogesterone caproate: implications for obstetrical practice. *Am. J. Obstet. Gynecol.* 208, 421–426 (2013).
3. Murphy, C. C., Cirillo, P. M., Krigbaum, N. Y. & Cohn, B. A. In utero exposure to 17α-hydroxyprogesterone caproate and risk of cancer in offspring. *Am. J. Obstet. Gynecol.* 226, 132.e1-132.e14 (2022).
4. Blackwell, S. C. *et al.* 17-OHPC to Prevent Recurrent Preterm Birth in Singleton Gestations (PROLONG Study): A Multicenter, International, Randomized Double-Blind Trial. *Am. J. Perinatol.* 37, 127–136 (2020).
5. Commissioner, O. of the. FDA Commissioner and Chief Scientist Announce Decision to Withdraw Approval of Makena. *FDA* https://www.fda.gov/news-events/press-announcements/fda-commissioner-and-chief-scientist-announce-decision-withdraw-approval-makena (2023).