EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 May 2024

EMA/263875/2024

Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

INN: hydroxyprogesterone caproate

Procedure number: EMEA/H/A-31/1528

Note:

Assessment report as adopted by the PRAC and considered by the CMDh with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Information on the procedure

In November 2021, a pharmaco-epidemiological study by Murphy et al was published in the literature, showing that in utero exposure to hydroxyprogesterone caproate (17-OHPC) may be associated with a higher risk of cancer in offspring. In addition, a large multicentre double-blind randomised controlled trial (RCT) conducted by Blackwell et al., was published in 2020, which concluded that 17-OHPC has no benefit over placebo in preventing recurrent threatened preterm labour in singleton gestations.

On 05 May 2023, France (ANSM) triggered a referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data and requested the PRAC to assess the impact of the above concerns on the benefit-risk balance of 17-OHPC-containing medicinal products and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

2. Scientific discussion

2.1. Introduction

17 α-hydroxyprogesterone caproate (17-OHPC) is a synthetic form of the naturally occurring hydroxyprogesterone. It is a derivative obtained by esterification with a hexanoic (caproic) acid at the C17α position. This chemical modification allows for different physiological properties and pharmacological profiles with respect to naturally occurring progesterone and its derivatives (Romero and Stanczyk, 2013; Feghali et al, 2014).

Despite widespread usage of 17-OHPC in the 1950s through 1970s, little information is known on the pharmacology of this substance. As a progestogen, it is supposed to mimic progesterone activity, such as having an anti-inflammatory effect and increasing local progestogen concentrations in gestational tissues, counteracting the functional decrease in progesterone that leads to preterm birth (Feghali et al, 2014). 17-OHPC binds to progesterone receptors, though with low affinity, acting as a progesterone agonist with improved pharmacokinetics and no other hormonal activity, thus exerting a prolonged progestogenic activity. Based on this property, 17-OHPC is expected to reduce the risk of pregnancy loss or premature labour in pregnant women and help treating certain gynaecological disorders related to a lack of progesterone such as menstrual irregularities. However, the effects of 17-OHPC on the uterine cervix in pregnant women, animals, and in the context of in-vitro experiments have not been widely studied compared to progesterone and conflicting evidence is available. The mechanism of action is not fully elucidated.

17-OHPC was approved in the 1950s. In the EU, it was first approved in Spain in 1955. Currently, 17-OHPC-containing medicinal products are authorised in Austria, France, and Italy as a solution for injection (250 mg/ml, 500 mg/2 ml and 341 mg/2 ml respectively). Depending on the Member States, the following obstetrical indications are authorised:

- risk of premature parturition associated with uterine hypermotility;
- habitual abortion due to corpus luteum deficiency, risk of abortion or prevention of repeat abortion demonstrated to be caused by a luteal phase defect, threat of miscarriage, recurrent miscarriage;
- protection of pregnancy in case of surgery.

They are also authorised in gynaecological indications as follows:

- luteal insufficiency, sterility due to a luteal phase defect;
- primary and secondary amenorrhea, artificial cycles in combination with an oestrogen;

- juvenile and climacteric dysfunctional metrorrhagia, disorders associated with progesterone deficiency (e.g. dysmenorrhoea, irregular menstrual periods, premenstrual syndrome, mastodynia).

In November 2021, a pharmaco-epidemiological study by Murphy et al was published in the literature, showing that in utero exposure to 17-OHPC may be associated with a higher risk of cancer in offspring.

In addition, a large multicentre double-blind RCT conducted by Blackwell et al was published in 2020, which concluded that 17-OHPC has no benefit over placebo in preventing threatened preterm labour in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth (PTB), neither for the mother (no extension of the duration of pregnancy) nor for the newborns (no reduction in serious events associated with prematurity). Based on the results of this RCT, the marketing authorisation in the United States of America (U.S.A.) for which this RCT was a confirmatory trial, was revoked in April 2023 on the grounds of lack of benefit.

On 05 May 2023, France (ANSM) triggered a referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data and requested the PRAC to assess the impact of the above concerns on the benefit-risk balance of 17-OHPC-containing medicinal products and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

The PRAC considered the available clinical and non-clinical data in relation to the risk of cancer in offspring exposed in utero to 17-OHPC as well as the available data on efficacy aspects pertinent to the indications authorised in the EU. In addition, the PRAC considered the responses from the authors of the study by Murphy et al, 2022 to questions from the Committee, as well as the views expressed by an ad-hoc expert group (AHEG). A summary of the most relevant information is included below.

2.2. Data on safety

The PRAC considered the results of the pharmaco-epidemiological study by Murphy et al, 2022 that examined the association between in utero exposure to 17-OHPC and the risk of cancer in offspring. In addition, the PRAC considered the responses from the authors of this study to questions from the Committee.

From the literature, the only publication evaluating this risk is that by Murphy et al, 2022. No other literature article or any MAH-sponsored study evaluates this issue. The study by Murphy et al, 2022 is further detailed below.

Searches in EudraVigilance and in the MAH(s) safety database retrieved a very limited number of individual case safety reports (ICSR) of cancer in offspring that did not allow to conduct signal detection analyses that could be meaningful in terms of causality assessment. From the ICSR retrieved (28), most of them were those from the study by Murphy et al, 2022 (23). Those did not add relevant information to the study by Murphy et al, 2022 and are not further discussed in this report.

Most of the available non-clinical safety studies were performed before the implementation of Good Laboratory Practice (GLP) rules and are not in line with contemporary testing standards. Besides, all studies present limitations, e.g. lack of exposure levels, lack of comparable findings in different species in terms of metabolic pattern of 17-OHPC. Overall, these studies did not inform on the risk of cancer development in the offspring.

2.2.1. Observational study

Murphy et al, 2022

The study by Murphy et al, 2022 is based on the Child Health and Development Studies (CHDS), a population-based cohort of more than 18,000 mother-child dyads receiving prenatal care in the Kaiser Foundation Health Plan (Oakland, California, U.S.A.) between 1959 and 1966, who were followed for 60 years. Incident cancers diagnosed in the offspring were ascertained through 2019 by linkage to the California Cancer Registry, one of the largest cancer registries in the U.S.A. meeting the quality data standards set by the National Program of Cancer Registries and the U.S.A. Center for Disease Control and Prevention (Killion et al, 2018; California Cancer Registry, Cancer reporting in California, 2021).

Method

In utero exposure to 17-OHPC was ascertained using the clinical information abstracted from mothers' medical records beginning six months prior to pregnancy through delivery. These records include prenatal visits, diagnosed conditions and prescribed medications. All medications are recorded with the date and conditions for which they were prescribed. Mothers who received 17-OHPC during pregnancy were identified and in utero exposure was measured as the trimester of first exposure (first trimester: 0–90 days; second trimester: 91–180 days; third trimester: ≥181 days). The total number of 17-OHPC injections (1–2 or ≥3 injections) was also measured.

Cox proportional hazards models were applied to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) to assess the association of in utero exposure to 17-OHPC and any cancer in offspring, overall and by trimester of first exposure and number of injections. The proportional hazards assumption was verified in all models by visually examining plots of the survival function versus survival time and in logrank tests for comparing survival curves. Follow-up time was accrued from date of birth through date of cancer diagnosis, date of death, or date of last contact. Cox proportional hazard models were also applied to all cancers combined and for specific cancer sites including prostate, colon and rectum, and paediatric brain cancers. Interaction between timing of in utero exposure to 17-OHPC and offspring sex was also explored by comparing nested models with and without early pregnancy by sex and late pregnancy by sex as interaction terms using a likelihood ratio test to assess effect modification.

Across all models, the following patient characteristics were evaluated a priori as confounders, individually and simultaneously: year of birth, sex, maternal age at pregnancy, race/ethnicity, maternal education, parity at pregnancy, total family income, gestational age (<37 weeks, ≥37 weeks), calculated maternal body mass index (BMI) and birth weight. These confounders were selected because they may be directly or indirectly related to the mothers' use of 17-OHPC and the offspring's risk of cancer.

In order to identify the most parsimonious model, only potential confounders that changed the effect estimate by >10% were retained, if removed from the model.

The following sensitivity analyses were also conducted by the authors:

- to assess confounding by indication, the association between any cancer in offspring and conditions indicating 17-OHPC in mothers was examined;
- to assess the impact of age of the offspring on the risk of cancer, Cox proportional hazards regression models were used by comparing the models with/without the interaction between the age at follow-up (+/− 50 years) and first exposure to 17-OHPC in the first trimester using a likelihood ratio test;

- to model errors from unmeasured confounding (e.g. shared factors between mother and offspring), a probabilistic bias analysis was performed;
- to deal with missingness of variables used in the models and ranging from 0.0% (birth weight, year of birth) to 13.3% (maternal BMI), multiple imputation was used.

Results

Among the 18,751 mother-child dyads from the CHDS cohort, half of the offspring were male and born in the early 1960s. 234 (1.2%) were exposed in utero to 17-OHPC and 18,517 not exposed. About 23.5% of the offspring exposed were non-Hispanic Black, and 36,5% with a family annual income less than the median, compared to respectively 18,8% and 32,6% of the not exposed. The median follow-up was 49.5 years (interquartile range (IQR): 25.5–53.5 years), without any difference between exposed (50.5 years) and not exposed (49.5 years) to 17-OHPC. The majority (70.5%) of offspring were first exposed in the first trimester, the first injection occurring at a mean of 12 weeks' gestation (median: 10 weeks, IQR: 7–15 weeks). There was a mean of 2.4 injections (median: 1 injection, IQR: 1–2 injections).

A total of 1,008 offspring were diagnosed with cancer over 730,817 person-years of follow-up. Approximately 1.2% of the offspring (n=234) were exposed in utero to 17-OHPC. Of the 234 individuals exposed in utero to 17-OHPC, 23 were diagnosed with cancer, including 2 diagnoses in childhood (age < 18 years) and 21 in adulthood (age >18 years). Median age at diagnosis was comparable for offspring exposed (45 years, IQR: 37 – 51 years) and not exposed (45 years, IQR: 34 – 51 years) to 17-OHPC.

Overall, offspring exposed in utero to 17-OHPC had an increased risk of any cancer (adjusted hazard ratios (aHR)=1.99 [95% CI 1.31-3.02]) compared to offspring not exposed, and the risk differed depending on the trimester of first exposure. Exposure in the first trimester was associated with an increased risk of any cancer (aHR=2.57 [95% CI 1.59-4.15]), and the risk increased with the number of injections (1–2 injections: aHR=1.80 [95% CI 1.12-2.90]; ≥3 injections: aHR=3.07 [95% CI 1.34-7.05]). See table 1 below.

Table 1. Adjusted HRs and incidence rates (per 100,000 persons) for any cancer in the offspring with and without 17-OHPC exposure, overall and by the trimester of first exposure and the number of injections.

Variables	Person-y	n	aHR[a]	95% CI	Incidence rate (95% CI) per 100,000[b]
In utero exposure to 17-OHPC					
Not exposed	721,401.5	985	1.00		13.7 (12.8—14.5)
Any exposure	9415	23	1.99	1.31—3.02	24.4 (15.5—36.7)
Trimester of first 17-OHPC exposure					
Not exposed	721,401.5	985	1.00		13.7 (12.8—14.5)
First trimester	6073	18	2.57	1.59—4.15	29.6 (17.6—46.8)
Second trimester	2423	4	1.24	0.46—3.32	16.5 (4.5—42.3)
Third trimester	919	1	0.82	0.18—3.80	10.9 (0.3—60.6)
Number of 17-OHPC injections					
Not exposed	721,401.5	985	1.00		13.7 (12.8—14.5)
1—2 injections	8062	14	1.80	1.12—2.90	22.3 (13.2—35.3)
≥3 injections	1353	9	3.07	1.34—7.05	37.0 (12.0—86.2)

17-OHPC, 17α-hydroxyprogesterone caproate; *aHR*, adjusted hazard ratio; *CI*, confidence interval.

[a] Adjusted for year of birth and maternal body mass index (overweight vs others); [b] Incidence rates and 95% CIs were calculated on the basis of the discrete probability distribution for a binomial parameter.

There was not any statistically significant increased risk of any cancer when 17-OHPC was first administered in the second trimester (aHR=1.24 [95% CI 0.46–3.32]) or third trimester (aHR=0.82 [95% CI 0.18–3.80]). However, when the first exposure to 17-OHPC occurred in the second or third trimester (referred as 'late pregnancy' below), it was associated with a risk of cancer in male (aHR=2.59 [95% CI 1.07-6.28]) but not in female (aHR=0.30 [CI 0.04 -1.11]) offspring. See table 1 above and table 2 below.

Table 2. Interaction between in utero exposure to 17-OHPC (no exposure versus early pregnancy versus late pregnancy) and the offspring sex.

Offspring sex	In utero exposure to 17-OHPC	Person-y	n	Incidence rate (95% CI)	Stratum-specific aHR (95% CI)[a]
Male	Not exposed	376,390.5	380	10.1 (9.1—11.2)	1.00
	Early pregnancy	3284	8	24.4 (10.5—48.0)	2.75 (1.36—5.54)
	Late pregnancy	1436.5	4	27.8 (7.6—71.3)	2.59 (1.07—6.28)
Female	Not exposed	345,011	605	17.5 (16.2—19.0)	1.00
	Early pregnancy	2789	10	35.9 (17.2—65.9)	2.09 (1.13—3.87)
	Late pregnancy	1905.5	1	5.2 (0.1—29.2)	0.30 (0.04—1.11)

Interaction evaluated by comparing nested models with and without early pregnancy × sex and late pregnancy × sex product terms with the likelihood ratio test (*P* value=.04); *P* values of product terms: early pregnancy × sex (.05) and late pregnancy × sex (.58).

17-OHPC, 17α-hydroxyprogesterone caproate; *aHR*, adjusted hazard ratio; *CI*, confidence interval.

[a] Adjusted for birth year and maternal body mass index.

The risk of colorectal cancer (n=3 in exposed versus n=65 in non-exposed, aHR=5.51 [95% CI 1.73-17.59]), prostate cancer (analyses including male offspring only, n=3 in exposed versus n=53 in non-exposed, aHR=5.10 [95% CI 1.24-21.00]), and paediatric brain cancer (person-years at risk up to 18 years, n=2 in exposed versus n=7 in non-exposed, aHR=34.72 [95% CI 7.29-164.33]) was higher in offspring first exposed to 17-OHPC in the first trimester compared to offspring not exposed.

Based on supplementary information and additional analyses stratified by cancer types provided by the study authors, a positive correlation was shown between exposure and the risk of cancer in offspring in three (i.e. prostate, colon and rectum and paediatric brain) out of five cancer types that occurred overall twice or more in exposed offspring. For breast cancer in the female offspring population and melanoma cancers, there was no evidence that 17-OHPC exposure is associated with an increased risk of such cancers. This stratified analysis was not possible for other cancer types due to the small number of cases among those exposed to 17-OHPC (1 case only recorded for: cervix, lung and bronchus, thyroid, testis, kidney and renal pelvis, non-Hodgkin lymphoma, corpus uteri, Hodgkin lymphoma, miscellaneous, chronic lymphocytic leukaemia, oropharynx).

The results of sensitivity analyses (multiple imputation, probabilistic bias analysis) did not differ from those reported above. In addition, there was no association between any cancer in offspring and threatened abortion (aHR=1.09 [95% CI 0.84-1.41]).

In order to assess the effect of age at follow-up, models with and without the interaction with age at follow-up (+/−50 years) and first exposure to 17-OHPC in the first trimester were compared using a likelihood ratio test. There was no evidence of interaction (p-value from likelihood ratio test=0.40) observed. The authors concluded by stating that caution using 17-OHPC in pregnancy is warranted, given the possible link with cancer in the offspring.

2.2.2. Discussion on safety data

Murphy et al, 2022 stated that the CHDS enrolled 98% of eligible pregnant women who were members of the Kaiser Foundation Health Plan in the Oakland, California area between 1959 and 1966. Although CHDS is a very large prospective longitudinal cohort study, it is possibly not representative of the overall population (as most cohort studies) of pregnant women in the U.S.A. However, if non-representativeness can lead to a potential bias in means or percentages, such bias is not expected to be differential between exposed and non-exposed women. This is not considered nor expected to constitute a strong drawback to study associations between exposure and outcomes (Nohr and Liew, 2018).

The main indication reported for 17-OHPC use was threatened abortion (41% of women). Amongst the remaining indications, the following were the most reported: pregnancy confirmed (20%), false labour (5%) and symptoms of pregnancy (5%). Information on administered dose for each specific indication was not discussed by the authors. In addition, most of the offspring (70%) were first exposed in first trimester. At time of inclusion, between 1959 and 1966, the only obstetric indications authorised were dedicated to the first trimester (infertility with inadequate corpus luteum function and habitual and threatened abortion). As the majority of pregnancy loss (80%) occurs before 12 weeks of gestation, a first injection during the second trimester is expected to be rare and as a consequence, so is the number of incidental cancers. Nevertheless, exposure in the second or third trimester conferred an additional risk for male (aHR=2.59 [95% CI 1.07-6.28]) but not female (aHR=0.30 [95% CI 0.04-1.11]) offspring. This finding is described by the authors as 'unexpected but plausible'. According to their hypothesis, effects observed in the offspring are possibly dependent on the timeframe of exposure to an endocrine disruptor. Late exposure to 17-OHPC during male foetus sexual differentiation (testosterone secretion) might have an effect later on cancer development. However, it is worth noting that there was only one case among female offspring exposed during late pregnancy and only four cases among males, making these results less robust, especially for a study of interaction which usually requires a larger sample size than that required for a study of associations. Therefore, whereas early in utero exposure to 17-OHPC seems to be associated with cancer development later in the offspring, data on late pregnancy exposure to 17-OHPC and risk of cancer in the offspring are less robust. However, a risk cannot be excluded at any pregnancy stage.

In terms of completeness of cancer ascertainment, the study aimed at evaluating lifetime cancer risk between 1959 and 2019 in the CHDS cohort linked to the population-based California Cancer Registry as a unique source of information on cancer diagnoses. Publicly available information reports that the California Registry was created in 1985 and started collecting data in 1988. Therefore, there is an uncertainty whether any cancer that occurred prior to 1988 was collected in the California Cancer Registry. Moreover, the linkage of the CHDS cohort with the California Cancer Registry does not assure the completeness of cancer incidence ascertainment since offspring can have moved outside California, hampering the possibility to monitor any possible diagnosis or treatment received elsewhere.

Regarding missing data, the authors performed multiple imputations to account for missingness. The results of this sensitivity analysis are consistent with the main analysis (although with aHRs>1 closer to 1 with smaller lower bounds of the 95% CI). Thus, accounting for missingness by multiple imputations did not change the results and conclusions of the study.

The authors clarified that follow-up time was defined as the time accrued from date of birth through date of cancer diagnosis, date of death or date of last contact. The Cox proportional hazards regression model was applied to time to first cancer incidence as the event. Although censoring at death may be informative, the frequency of death at around 50 years of age is expected to be low. In addition, it is unlikely that such censoring is differential by exposure group. Moreover, the median follow-up is

comparable between exposure groups and it is unlikely that the relatively small difference in the proportion of patients achieving 50 years minimum of follow-up (54.7% in exposed versus 49.8% in non-exposed offspring) could explain the 2-fold increase in risk of cancer.

Maternal conditions/diseases related to indications for use of 17-OHPC treatment are likely to contribute as important confounders. The authors only controlled for birth year and maternal BMI. If removed from the model, these two confounders are those that changed the effect estimate by more than 10%. The authors also considered the impact of the offspring age on the risk of cancer by taking into account the age at follow-up +/- 50 years, though this stratification could not be sufficiently detailed to capture the differential age structure between exposed and not exposed. In addition, indication bias is still possible. For instance, maternal smoking may be associated with a risk of miscarriage, that can encourage the use of treatment with 17-OHPC. Maternal smoking may also be associated with passive smoking during childhood or an increased risk in the offspring to smoke at a later life stage. This would imply a higher risk of cancer in offspring of women treated for the miscarriage indication. However, the authors stated that the main indication for 17-OHPC use (repeated or imminent abortion, 41% of women exposed) is itself not associated with a risk of cancer in the offspring. In addition, no information is available on possible exposure of women to diagnostic procedures such as x-ray (common in the 1960s) or other substances known to have cancerogenic activity (e.g. dicyclomine, diethylstilbestrol (DES)). Specifically, DES was marketed in the U.S.A. during the same period and was also used for the prevention of miscarriage. However, such a confounding effect would mean that most of the cancers retrieved in both study groups are mainly hormonal-dependent, which is not the case.

Regarding possible residual confounding, the authors considered that in view of the study results, a treatment-related factor independent of the risk of miscarriage could be expected. Therefore, a probabilistic bias analysis was performed as a sensitivity analysis to test the robustness to such unmeasured confounding. This analysis showed no evidence of any impact of any bias due to unmeasured confounding factors. Therefore, there is no evidence supporting the view of the AHEG that the study findings could also be due to other factors the study did not investigate (see section 3 on expert consultation).

The PRAC noted the view of the AHEG that potential mechanisms are unclear which is further hindered by the long-time gap between potential exposure of the mother and the development of cancer in offspring. The mechanisms underlying a potential increase in cancer risk among offspring exposed to 17-OHPC during embryo-foetal development have yet to be elucidated. Within the existing literature, various pharmacodynamic and pharmacokinetic hypotheses have been explored, however no specific mechanism is identified with 17-OHPC.

Therefore, the PRAC considered that the lack of identified plausible mechanisms underlying this potential risk did not allow to exclude it.

The AHEG also highlighted a linearity in the increased risk of cancer with the number of injections suggesting a dose-dependency. The risk is already statistically significant after 1 single injection (aHR=1.80 [95% CI 1.12-2.90]) with no safe threshold identifiable. In addition, no mechanism is identified precluding from further determining the conditions under which 17-OHPC should be considered a cancer hazard. Moreover, treatment schedule in obstetrical indications (imminent and habitual abortion, risk of PTB, protection of pregnancy in case of surgery) and gynaecological indications falls within the variables associated with an increased risk. The same applies to the indication of ‘infertility due to corpus luteum insufficiency’ where the use of 17-OHPC in support of the luteal phase is protracted through the first trimester to sustain pregnancy.

The PRAC identified several notable strengths in the design of the study by Murphy et al, 2022, i.e. it is a large, well-established, and population-based health-care registry, with variables of the exposure and outcome with low risk of misclassification and a long and intergenerational follow-up.

It is noted however, as also pointed out by the AHEG, that the number of cases across various types of cancer is low and that cancer development over a human lifetime is multifactorial. As in any observational study, residual confounding remains possible.

Nonetheless, the statistical methods applied were appropriate (adjustment, probabilistic bias analysis, testing for confounding by indication, multiple imputation of missing data) and it is unlikely that any residual confounder may have a significant impact on the study conclusions.

The PRAC considered the view of the AHEG that the study findings could not be translated into a causal association due to the multiple possible biases. Nevertheless, the PRAC considered that these were partially controlled through adjustment and investigated through sensitivity analysis and concluded that the risk of cancer in offspring exposed in utero to 17-OHPC is a potential risk.

In addition, while most of the study population was exposed during the first trimester of pregnancy, the risk cannot be excluded for any exposure occurring during the second and third trimesters. Therefore, the study results impact all indications where an exposure in utero to 17-OHPC is possible.

It was also noted that this is the only available study exploring this risk and hence, the only piece of evidence concluding on an association between 17-OHPC exposure in utero and an increased risk of cancers in offspring. Nonetheless, this does not affect the relevance of the results.

Finally, the PRAC noted the view from one of the experts of the AHEG that should a causal association be established, this might also be potentially relevant for other products of the class, However, considering the different pharmacological properties of 17-OHPC compared to progesterone and other progestogens, and in light of the study results, the risk cannot be extrapolated to progesterone.

2.2.3. Risk minimisation measures

In order to minimise the potential risk of cancer in offspring exposed in utero to 17-OHPC, measures to prevent in utero exposure to 17-OHPC were explored.

In all obstetric indications, 17-OHPC is administered during pregnancy. Depending on the indication, 17-OHPC injection can be administered weekly or up to every 2 days. Drug plasma concentrations increase with repeated injections. During pregnancy, 17-OHPC crosses the human placenta, and the drug can be detected in both maternal and foetal blood up to 44 days after the last injection (Vidaeff and Belfort, 2013). The terminal half-life of 17-OHPC is reported to be about 8 days in non-pregnant women and increases to up to 16 days (±6 days) in pregnant women. Indeed, 17-OHPC is slowly released due to its formulation with castor oil, and the slow release is also maternal fat dependent (Caritis et al, 2012). In addition, variability is observed in 17-OHPC-plasma concentrations at the same dosing regimen depending on the BMI of women and their body fat mass. Obese women tend to have lower plasma concentrations (Caritis et al, 2011). Therefore, in all obstetric indications, preventing exposure to 17-OHPC in utero is not possible.

In the indications of 'luteal insufficiency' and 'sterility due to a luteal phase defect', 17-OHPC is used in the context of in vitro fertilisation (IVF) treatment to support the luteal phase in order to facilitate the implantation of embryo(s) and the continuation of pregnancy during the first trimester. The first injection of 17-OHPC is done at day 16 of the menstrual cycle. 17-OHPC can be injected once to twice

a week generally until the twelfth week of pregnancy. Therefore, administration of 17-OHPC is expected during pregnancy during at least the first trimester. Hence, in utero exposure to 17-OHPC cannot be avoided in those indications. The AHEG's consideration to limit the use of 17-OHPC up to a positive pregnancy test was considered. However, in case of treatment discontinuation as soon as a pregnancy test turns positive, this does not prevent embryo's exposure in utero to 17-OHPC as the drug can be retrieved in foetal circulation up to 44 days after the last injection.

In the gynaecological indications of 'juvenile and climacteric dysfunctional metrorrhagia', 'disorders associated with progesterone deficiency (e.g. dysmenorrhoea, irregular menstrual periods, premenstrual syndrome, mastodynia)', 'primary and secondary amenorrhea' and 'artificial cycles in combination with an oestrogen', 17-OHPC administration aims to mimic the luteal phase in women with cycle's disorders. Depending on the indication, 17-OHPC injection is done either at day 16 or between day 18 and day 20 of the menstrual cycle. The PRAC noted the view from the AHEG that any exposure to 17-OHPC during pregnancy when used in such indications is expected to be very low as unintended pregnancies are unlikely to occur in patients treated with 17-OHPC. However, in the indications of metrorrhagia and dysmenorrhoea (including other disorders associated with progesterone deficiency), women are of childbearing age. As for the indications of amenorrhea and artificial cycles, a pregnancy cannot be excluded because either pregnancy is the goal (e.g. assisted reproductive technology (ART)) or amenorrhea is effectively corrected and therefore allows for a pregnancy to occur (intended or not). Therefore, the PRAC considered that 17-OHPC administration during or in close temporal relation to pregnancy can occur in these indications. Indeed, a pregnancy is possible in the days following 17-OHPC administration during the second part of the cycle. Considering the long half-life of 17-OHPC which varies from 8 days in non-pregnant women to 16 days in pregnant women, the fact that 17-OHPC crosses the placenta and that 17-OHPC is retrieved in foetal circulation up to 44 days after the last injection, embryo-foetal exposure can last for at least 1 month post 17-OHPC administration until the drug is fully eliminated. Therefore, measures to prevent pregnancy during or shortly after treatment and in turn in utero exposure to 17-OHPC were further explored. As 17-OHPC is a hormonal treatment, it is not possible to use a hormonal contraception since the combination of two hormonal treatments is not recommended either due to accumulation of metabolic/vascular risks or due to the risk of drug-drug interactions. Alternative options include the use of mechanical contraceptive methods such as copper intra-uterine devices (Cu IUDs). However, Cu IUDs are not adequate for women with metrorrhagia or dysmenorrhoea as they enhance their symptoms. An additional barrier method such as condoms is a less effective contraceptive method (85% versus 99% for Cu IUDs) and, even if complemented by regular pregnancy tests, these measures would not prevent embryo's exposure to 17-OHPC in case of pregnancy due to the long half-life of the drug. Therefore, these measures were not considered sufficient to prevent in utero exposure to 17-OHPC.

2.3. Data on efficacy

The MAHs were requested to submit available data to support the efficacy of their medicinal products in their authorised indications. In addition, a further literature search was performed.

2.3.1. Clinical trials and meta-analyses in the prevention of preterm birth

The trials by Meis et al, 2003 and Blackwell et al, 2020 conducted in the prevention of pre-term labour were identified as the most relevant, together with several meta-analyses published more recently on the efficacy of progestogens, including 17-OHPC, in the prevention of pre-term labour. These are further detailed below.

Meis et al, 2003 and Blackwell et al, 2020 (PROLONG study)

Meis et al, 2003

The study by Meis et al, 2003 was a double-blind, placebo-controlled trial involving pregnant women with a documented history of spontaneous preterm delivery. 463 women were enrolled at 19 clinical centres at 16 to 20 weeks of gestation and randomly assigned in a 2:1 ratio to receive either weekly injections of 250 mg of 17-OHPC or weekly injections of an inert oil placebo. In this study a statistically significantly lower rate of delivery prior to 37 gestational weeks was observed in the treatment arm receiving 17-OHPC 250 mg injection than the placebo arm.

Blackwell et al, 2020 (PROLONG study)

The study by Blackwell et al, 2020 also known as the PROLONG study is an international multicentre, randomised, placebo-controlled, double-blind trial recruiting women ≥ 18 years old, with a singleton pregnancy who had a documented previous pregnancy complicated by a singleton spontaneous preterm delivery and who were 16 to 20 weeks in the current pregnancy. The study had two co-primary efficacy endpoints, namely PTB before 35 gestational weeks and composite neonatal morbidity and mortality index. Overall, 1,708 eligible patients for the study were randomised to 17-OHPC 250 mg (n=1,130) and to placebo (n=578) given weekly from 16 to 20 gestational weeks until 37 weeks or delivery (whichever the earliest). The planned sample size was achieved. Russia, Ukraine and the U.S.A. were the three highest enrolling countries, randomising 621 (36%), 420 (25%) and 391 (23%) subjects respectively and data were provided for 1,651 liveborn neonates. The 17-OHPC and placebo groups were balanced across all reported demographics, baseline characteristics, and obstetrical characteristics in the current and previous pregnancies.

There was no significant difference in either PTB before 35 weeks (17-OHPC 11.0% versus placebo 11.5%; relative risk (RR)=0.95 [95% CI 0.71–1.26]) or composite neonatal index (5.6% versus 5.0% RR=1.12 [95% CI 0.68–1.61]) between the two groups. Similarly, the rate of PTB <37 and <32 weeks were not different between the groups. There were also no differences in maternal outcomes including the need for cerclage placement, tocolysis, antenatal corticosteroid therapy, gestational diabetes, preeclampsia, chorioamnionitis and abruption. In addition, there was no evident numerical separation between 17-OHPC and placebo in terms of the point estimate of the treatment difference for these efficacy endpoints. Therefore, 17-OHPC did not decrease recurrent PTB.

Discussion

In 2011, based on the results of the study by Meis et al, 2003, the United States Food and Drug Administration (FDA) granted a conditional approval for a 17-OHPC-containing medicine indicated in the reduction of the risk of PTB in women with a singleton pregnancy who have a history of singleton spontaneous PTB. This conditional approval was granted with the obligation to conduct a confirmatory trial, the PROLONG study by Blackwell et al, 2020.

In the study by Meis et al, 2003 the primary endpoint was preterm delivery prior to 37 completed weeks of gestation. The sample size was calculated to estimate the effect of 17-OHPC on this outcome. The clinical trial was not designed to assess the effect of 17-OHPC on the neonates. The treatment groups were not strictly comparable as the placebo group encompassed more women at higher risk of PTB (due to a higher proportion of previous PTB) compared to the 17-OHPC group (41.2% in placebo versus 27.7% in 17-OHPC treatment group). Furthermore, uncertainties were raised regarding the results of this study because of the unexpected high rate of PTB in both the placebo and the 17-OHPC arms compared to other studies. Uncertainties also related to findings reported in early enrolled patients that were not included in the final analysis.

The PROLONG study by Blackwell et al, 2020 showed a much lower than expected event rate and a limited number of patients with short cervix that might challenge the assessment of treatment effects. However, the study population was around four times higher than the study of Meis et al, 2003. Moreover, a planned pre-specified subgroup analysis showed in the U.S.A. only subgroup non-significant trends for treatment efficacy with PTB <32 weeks and <35 weeks and for the composite neonatal morbidity and mortality index. Moreover, another sub-analysis showed that when stratifying patients according to their risk of PTB (high or low) there was no efficacy of 17-OHPC in any sub-groups. Nevertheless, despite some limitations such as the high population recruitment outside the U.S.A. (75%), the PROLONG study is an adequately designed placebo-controlled study using a large sample size with a low rate of loss to follow-up which demonstrated a lack of efficacy of 17-OHPC versus placebo in the reduction of PTB and neonatal complications in women with previous PTB.

The two studies by Meis et al, 2003 and Blackwell et al, 2020 present several differences between the enrolled populations. However, the PROLONG study protocol substantially mirrored the trial by Meis et al, 2003 which allowed for comparisons between the two studies. While the trial by Meis et al, 2003 included 27% of women with >1 previous PTB, this category of randomised women at very high risk of PTB represented 13.1% only in the study of Blackwell et al, 2020. However, the proportion of women at high risk of PTB in Blackwell et al, 2020 was comparable between the 17-OHPC and placebo groups (respectively 13.1 % versus 12.1%) whereas in Meis et al, 2003, there was an imbalance between the two groups (27.7% versus 41.2%). Sub-analyses showed that 17-OHPC had no effect either in the highest risk population or the lowest one, and did not find any population that would benefit from 17-OHPC. In the study by Blackwell et al, 2020, 75% of women were recruited outside the U.S.A. precluding the comparison with the results of Meis et al, 2003 which included U.S.A. women only. However, the U.S.A. population (n=391 women) in Blackwell et al, 2020 was comparable to the total sample size of Meis et al, 2003. Moreover, the sub-analyses showed no evidence of a treatment effect among the U.S.A. or non-U.S.A. participants. Geographic differences do not explain the contradictory results (Chang et al, 2020). These differences in recruitment or in baseline risk of PTB between the studies of Meis et al, 2003 and Blackwell et al, 2020 do not explain the differences in their findings. Overall, the study by Blackwell et al, 2020 is considered as well designed and adequately powered to detect any possible effect of 17-OHPC in the reduction of PTB or neonatal complications. These findings led in 2023 to the revocation of the 17-OHPC-containing medicine that was authorised under conditional approval in the U.S.A.

Stewart et al, 2021

The 'Evaluating Progestogens for Preventing Preterm-birth International Collaborative' (EPPPIC) project conducted a meta-analysis of individual participant data from 31 randomised controlled trials evaluating the efficacy of various progestogens with different routes of administration (vaginal progesterone, oral progesterone, intramuscular 17-OHPC) to reduce the risk of PTB in at-risk women with singleton or multifetal pregnancies. These include 15 clinical trials specific to 17-OHPC, of which 5 trials (including the above-mentioned trials by Meis et al, 2003 and Blackwell et al, 2020) assessed singleton pregnancies comparing 17-OHPC to either placebo (n=4) or progesterone (n=1).

The trials relating to 17-OHPC studied two main PTB-related risk factors, namely short cervix and history of PTB. Only one trial studied a combination of short cervix and another risk factor (i.e. prior history of PTB, uterine malformations, cervical surgery, or prenatal DES exposure). The observed reduced risk of early PTB (<34 weeks gestation) in singleton pregnancies (RR= 0.83 [95% CI 0.68–1.01]) for 17-OHPC compared with control showed a positive trend but did not reach statistical significance. Sub-analyses performed by main risk factor type (history of PTB or short cervix or combination of both) showed that 17-OHPC had no effect in any subpopulation at risk. The meta-

analysis also includes 8 clinical trials in multifetal pregnancies mostly in women without additional risk factors. 17-OHPC did not reduce PTB before 34 weeks for twins or triplets (2,253 women; RR=1.04, [95% CI 0.92–1.18]).

It is noteworthy that this meta-analysis studied several risk factors of PTB including the most frequent ones (history of PTB or short cervix, multiple pregnancy). Despite the heterogenicity of women risk factors, the data pooled together did not show any statistical superiority of 17-OHPC versus comparator (placebo or progesterone). When taken independently, the sub-analyses failed to demonstrate any efficacy of 17-OHPC in the prevention of PTB (≤34 weeks of gestation) in any population of women at risk of PTB.

Care et al, 2022

Care et al, 2022 is a meta-analysis including more than 20 clinical trials comparing the efficacy of 17-OHPC to either placebo or standard of care of progesterone in the prevention of spontaneous PTB in women with singleton pregnancy. The populations studied were pregnant women (singleton) at risk of PTB (personal history of PTB, short cervix, cervical insufficiency) and the outcomes were the number of PTB <37 or <34 or <28 weeks of gestation as well as neonatal death and morbidities. While the studies by Meis et al, 2003 and Blackwell et al, 2020 were included, there were more trials focussed on singleton pregnancies than in the EPPPIC meta-analysis. The overall quality of this meta-analysis is considered less robust than the EPPPIC meta-analysis due to the heterogeneity of the studies, certain with a risk of bias. The meta-analysis did not demonstrate a higher efficacy of 17-OHPC versus placebo neither in the prevention of PTB in women at high risk of PTB (odd ratio (OR)=0.68 [CI 95% 0.43-1.02]) nor in the reduction of neonatal deaths (OR=0.78 [CI 95% 0.50-1.21]).

Ferrari et al, 2023; Breuking et al, 2023

In these two meta-analyses, the authors studied the effect of 17-OHPC in the maintenance of pregnancy in women who received tocolysis during pregnancy of a preterm labour episode. The same set of clinical trials (except for one) were included in the two meta-analyses. As the meta-analyses had different objectives from the clinical trials of Meis et al, 2003 or Blackwell et al, 2020, those were not included. Ferrari et al, 2023 found that 17-OHPC significantly reduced PTB <34 weeks (RR=0.72 [95% CI 0.54-0.95], 450 participants), but the results were not consistent across all analyses and other endpoints (PTB < 37 weeks). As the clinical trials included in the meta-analysis are at high risk of bias and the protocols were not always fully available, the authors concluded that the results are insufficient to generate recommendations in clinical practice. Breuking et al, 2023 did not differentiate 17-OHPC from progesterone in the results and, when only clinical trials with a low risk of bias were considered, the authors concluded on a lack of efficacy of progestogens on the prolongation of latency time until delivery.

2.3.2. Data in other indications

In the indications other than the risk of premature parturition, the available efficacy data are either limited, of low quality and/or not conducted in line with the current standards.

In the indications of 'habitual abortion due to corpus luteum deficiency', 'risk of abortion or prevention of repeat abortion demonstrated to be caused by a luteal phase defect', 'threat of miscarriage' and 'recurrent miscarriage', limited efficacy data was available, mostly from the time of the initial marketing authorisations. At the time, studies were considerably less standardised than would be necessary today and would not fulfil contemporary requirements regarding validated endpoints, statistical confirmation, or Good Clinical Practice (GCP). Several recent meta-analyses (Saccone et al, 2017; Wahabi et al, 2018, Haas et al, 2019, Devall et al, 2021) include a limited number of those

clinical trials. The meta-analysis of Saccone et al, 2017 focused on the prevention of miscarriage only and found a statistical lower rate of miscarriage in the 17-OHPC arm versus placebo (RR=0.69, [95% CI 0.35–0.88]). However, the clinical trials in this meta-analysis were not designed to assess 17-OHPC in this indication, not randomised, or otherwise of low quality. Therefore, these were not selected in the later meta-analyses. The meta-analyses by Devall et al, 2021 failed to demonstrate a benefit of 17-OHPC in the prevention of recurrent miscarriage/habitual abortion, due to a limited number of studies, and in threatened abortion/imminent miscarriage, due to the absence of data. These results are in line with the findings of the meta-analyses of Wahabi et al, 2018 and Haas et al, 2019. Overall, a limited number of studies is available, all presenting methodological issues, and more recent meta-analyses could not demonstrate a benefit of 17-OHPC, which cast doubts on the efficacy of 17-OHPC in these indications.

Uncertainties are also attached to the results of the scarce efficacy studies of 17-OHPC in the indications of luteal insufficiency, sterility due to a luteal phase defect. These do not meet the current standards in terms of design and statistical analysis.

No study evaluating the efficacy of 17-OHPC in the gynaecological indications and in the indication of protection of pregnancy, could be identified.

2.3.3. Discussion on efficacy

The effect of 17-OHPC in the prevention of PTB was studied through the clinical trials and meta-analyses mentioned above in women at risk of PTB. Despite the findings by Meis et al, 2003 showing a statistically significantly lower rate of delivery prior to 37 gestational weeks in the treatment arm receiving 17-OHPC compared to placebo in women with a history of PTB, these could not be reproduced in the results of the confirmatory trial by Blackwell et al, 2020 that showed no decrease in recurrent PTB, nor on the composite neonatal index. The study by Blackwell et al, 2020 encompassed a population four times higher than that of Meis et al, 2003 and was adequately powered and designed to assess effect of 17-OHPC on reduction of PTB and complication in neonates. Taken together with the meta-analyses that explored the risk of PTB with other risk factors, these did not show efficacy in the prevention of PTB regardless of PTB-related risk factors. In the EU, 17-OHPC is authorised for the indication of 'risk of premature parturition associated with uterine hypermotility'. This indication seems to be related to a broad spectrum of nosologically defined clinical entities and the posology is not clearly defined in term of dosage and frequency of administration with different approaches based on empirical considerations. As the population of women encompassed in this indication is heterogenous and cover all PTB-related risk factors, it is considered that the results of the clinical trial by Blackwell et al, 2020 and the meta-analyses mentioned above are sufficiently representative of the different possible risk factors linked to PTB. Therefore, these new efficacy data could not reproduce the previously demonstrated benefit of 17-OHPC-containing medicinal products in the indication 'risk of premature parturition associated with uterine hypermotility', and are considered to show a lack of efficacy.

Further, the PRAC noted that there is limited data on efficacy in other obstetrical and gynaecological indications for which 17-OHPC is authorised. The limitations and uncertainties attached to these datasets hinder the ability to draw robust conclusions on the efficacy. For these reasons, studies conducted after the initial marketing authorisations do not provide new significant scientific data on the efficacy of 17-OHPC in these indications.

It was noted that the AHEG was not aware of any national or international guidelines in both the gynaecological and obstetrical fields recommending 17-OHPC. No European guideline recommending the use of 17-OHPC in these indications was identified in the review.

3. Expert consultation

The PRAC consulted an ad-hoc expert group which provided advice on a number of issues. The AHEG answers are presented below.

Question 1-a: what is the place in therapy and the medical need of 17-OHPC for all authorised indications in the EU?

The experts noted that 17-OHPC is only available in a limited number of EU Member States and has a limited use. In many Member States, 17-OHPC is either not available any longer or has never been used.

The experts were not aware of any national or international guidelines in both the gynaecological and obstetrical fields recommending 17-OHPC. It was however noted that 17-OHPC is used in the context of infertility treatment, risk of abortion or contractions in the countries where it is authorised.

For the gynaecological indications, including luteal phase support in the context of IVF, the experts noted that 17-OHPC is not commonly prescribed, especially as there are other progesterone products available for oral and vaginal use. To their knowledge, while some reports show therapeutic superiority of the effects of 17-OHPC over other products authorised for these indications, systematic reviews have not found evidence favouring 17-OHPC administration for IVF treatment.

For the obstetrical indications, the experts were of the view that there is no clear need to use 17-OHPC and treatment alternatives with higher efficacy exist. For premature labour and short cervix, from the progestogen class, only micronised progesterone taken orally or vaginally is included in national treatment guidelines but stated as a consideration rather than a recommendation.

The experts also discussed that pregnant women at risk of spontaneous abortion (and history of previous spontaneous abortions or preterm birth) and who present with vaginal bleeding could benefit from injectable 17-OHPC, as vaginal progesterone will not reach the uterus during episodes of heavy bleeding. However, oral micronised progesterone is a more prescribed alternative in this indication.

17-OHPC is to be administered by injection via the intramuscular route and some experts acknowledged that this could be an advantage compared to a vaginal route that can be arduous for some patients. 17-OHPC also ensures treatment compliance as injection(s) are done in clinical setting. However, one expert expressed that patients would generally prefer the vaginal or oral route of administration because of the pain experienced with the injection route. From a patient perspective, it would be important to take patient individual preferences into account.

Question 1-b: are there any specific patient populations for which 17-OHPC is the only therapeutic option available in clinical practice?

The experts could not identify any specific patient populations for which 17-OHPC is the only therapeutic option. 17-OHPC might theoretically be necessary for some patients, for example in case of allergy to excipients of alternative formulation, or poor compliance to oral or vaginal formulations. However, the experts were of the opinion that such group of patients is very small.

Question 2-a: given the observed higher incidence of cancer in offspring exposed to 17-OHPC during pregnancy (Murphy et al, 2022), please discuss the relevance and impact of these findings for each obstetrical and gynaecological indication authorised in the EU in view of the targeted populations (women of childbearing potential, pregnant women, premenopausal women)?

The experts noted that the study authors concluded on an association between exposure of 17-OHPC in pregnancy and certain cancers in offspring, which was found to be statistically significant in the first trimester only and appeared to be dose dependent. However, the experts considered that these findings cannot be translated into a causal association. They also highlighted that cancer development over a human lifetime is multifactorial. In addition, in view of the multiple possible biases and the low number of cases across various types of cancer, the experts considered that the study findings could also be due to other factors the study did not investigate. It was also noted that this is the only available study exploring this risk and hence, the only piece of evidence concluding on an association between 17-OHPC exposure in utero and an increased risk of cancers in offspring. The experts considered that potential mechanisms are unclear and these are further hindered by the long-time gap between potential exposure of the mother and the development of cancer in offspring. One expert however raised that should a causal association be established in the future, this might also be potentially relevant for other products of the class.

In absence of clear data, the experts opposed the idea of any dedicated communication (e.g. DHPC) on study results mentioning the risk of cancer in offspring, since this may have a profound impact on exposed parents and their children over their lifetimes. Without robust evidence, there could be a risk of a potential false alarm raising possible anxiety among women treated with 17-OHPC and their offspring exposed in utero. Therefore, the experts were of the view that careful consideration should be given in this respect.

The patient representative posed the question if further research could be conducted in the EU as a second trial similar to Murphy et al. looking into historical data. However, some experts questioned the feasibility of such a study in view of the already low use of 17-OHPC and considered it of limited value for future patients, especially as the product is rarely used now, and in case indication(s) are removed as an outcome of the current review. However, the need for a trial could be revisited in the future, e.g. in case there is a new marketing authorisation, a new indication.

Question 2-b: are there any measures you would consider warranted to reduce the risk of foetal exposure in any of the authorised obstetrical indications?

The experts reiterated that the exposure to 17-OHPC is already limited in the EU and from their experience, alternatives are usually preferred. No further measures than limited exposure were proposed by the experts.

Question 2-c: are you of the opinion that the risk of cancer in offspring found by Murphy et al, 2022 needs to be mitigated in the gynaecological indications?

The experts highlighted again the low use of 17-OHPC in the gynaecological indications. They were of the view that any exposure to 17-OHPC during pregnancy when used in such indications is expected to be very low as unintended pregnancies are unlikely to occur in patients treated with 17-OHPC.

In the indication linked to IVF, 17-OHPC is used for luteal phase support in association with the transfer of a fresh or frozen-thawed embryo. To limit exposure during pregnancy, the experts considered that 17-OHPC should not be administered beyond a positive pregnancy test. If there is need for luteal support after a positive pregnancy test, alternative formulation(s) would be preferred.

4. Benefit-risk balance

17 α-hydroxyprogesterone caproate (17-OHPC) is a synthetic form (ester) of the naturally occurring hydroxyprogesterone. It is a derivative obtained by esterification with a hexanoic (caproic) acid at the C17α position.

The PRAC reviewed the totality of the data available for 17-OHPC-containing medicinal products in relation to the risk of cancer in offspring exposed in utero to 17-OHPC as well as the available efficacy data pertinent to the indications authorised in the EU. The PRAC assessed their impact on the benefit-risk balance of those products. This included the responses submitted by the marketing authorisation holders (MAHs) in writing, data submitted during the review by the authors Murphy et al, 2022 as well as the views expressed by an ad-hoc expert group (AHEG).

With respect to safety, the only relevant study found in the literature exploring the risk of cancer in offspring exposed in utero to 17-OHPC is that by Murphy et al, 2022. This study is a very large database cohort study linked to a cancer registry, with a long and intergenerational follow-up showing a statistically significant 2-fold increased risk of cancer in offspring exposed in utero to 17-OHPC. Notwithstanding the low number of cases and potential remaining non-controlled confounders, the PRAC considered that the risk of cancer in offspring exposed in utero to 17-OHPC is a potential risk.

Despite the lack of identified plausible mechanisms underlying this potential risk, the PRAC considered that the risk was possible. In addition, most of the study population was exposed during the first trimester of pregnancy. Nonetheless, the risk of cancer in offspring exposed in utero to 17-OHPC cannot be excluded for any exposure occurring during the second and third trimesters. Therefore, this potential risk is of relevance in all therapeutic indications where an exposure in utero to 17-OHPC is possible.

Due to the different pharmacological properties of 17-OHPC compared to progesterone and other progestogens, and in light of the study results, the risk cannot be extrapolated to progesterone.

With respect to efficacy, the PRAC considered the results of the trials by Meis et al, 2003 and Blackwell et al, 2020 (PROLONG study) and meta-analyses in the context of available efficacy data on 17-OHPC-containing medicinal products pertinent to the indication on the prevention of premature parturition. The results of the PROLONG study showed a lack of efficacy of 17-OHPC in women with singleton history of preterm birth (PTB) versus placebo in the reduction of PTB and neonatal complications in women with previous PTB. In other subpopulations at risk of PTB, recent meta-analyses (Stewart et al, 2021; Care et al, 2022) showed that 17-OHPC has no efficacy regardless of PTB-related risk factors. Further, the PRAC noted that there is limited data on efficacy in other obstetrical and gynaecological indications for which 17-OHPC is authorised.

The PRAC considered possible measures to minimise the potential risk of cancer in offspring exposed in utero to 17-OHPC, through avoiding in utero exposure to 17-OHPC. This discussion was guided by the following considerations: 1) during pregnancy, placental transport of and foetal exposure to 17-OHPC has been demonstrated, 2) 17-OHPC crosses the human placenta, and the drug is detectable in both maternal and foetal blood for at least 44 days after last injection, 3) the terminal half-life of 17-OHPC is reported to be about 8 days in non-pregnant women and increases up to 16 days (±6 days) in pregnant women. Therefore, in utero exposure to 17-OHPC can only be avoided if treatment can be interrupted sufficiently in advance of a pregnancy. Since 17-OHPC is administered during pregnancy in the obstetric indications, it was not considered possible to minimise the potential risk of cancer in offspring in such indications.

In the indication on the 'risk of premature parturition associated with uterine hypermotility', the PRAC considered that the benefit-risk balance of 17-OHPC-containing medicinal products is negative in view of the potential risk of cancer in offspring exposed in utero taken together with the evidence from the recent efficacy data detailed above.

Regarding the other obstetrical indications, in view of the potential risk of cancer in offspring exposed in utero which can only be minimised by avoiding exposure during pregnancy, taken together with the limited number of efficacy studies, all presenting methodological issues in the indications of 'habitual and imminent abortion due to corpus luteum deficiency', 'threat of miscarriage, recurrent miscarriage' and the absence of efficacy data in the indication of 'protection of pregnancy in case of surgery', the Committee considered that the benefit-risk balance of 17-OHPC-containing medicinal products in these indications is negative.

In the indication of 'luteal insufficiency' and 'sterility due to a luteal phase defect', 17-OHPC is used in the context of in vitro fertilisation (IVF) treatment to support the luteal phase to facilitate the implantation of embryo(s) and the continuation of pregnancy during the first trimester. The first injection of 17-OHPC is done at day 16 of the menstrual cycle and injections can be done once to twice a week generally until the twelfth week of pregnancy. Therefore, the potential risk of cancer in offspring exposed in utero is relevant in these indications as administration of 17-OHPC can be expected during the first months of pregnancy. The AHEG considered that in this population, administration could be limited to the period until a positive pregnancy test is obtained. However, considering the long half-life of 17-OHPC and that 17-OHPC is retrieved in foetal circulation up to 44 days after the last injection, even if treatment with 17-OHPC is stopped at the time of a positive pregnancy test, it would not avoid embryo-foetal exposure. Taking these into account and considering the limited efficacy data, the Committee considered that the benefit-risk balance of 17-OHPC-containing medicinal products in the indications of 'luteal insufficiency' and 'sterility due to a luteal phase defect' is negative.

In the gynaecological indications of 'juvenile and climacteric dysfunctional metrorrhagia', 'disorders associated with progesterone deficiency (e.g. dysmenorrhoea, irregular menstrual periods, premenstrual syndrome, mastodynia)', 'primary and secondary amenorrhea' and 'artificial cycles in combination with an oestrogen', 17-OHPC administration aims to mimic the luteal phase in women with cycle's disorders. 17-OHPC injection is done either at day 16 or between day 18 and day 20 of the menstrual cycle. The PRAC noted the view from the AHEG that any exposure to 17-OHPC during pregnancy when used in such indications is expected to be very low as unintended pregnancies are unlikely to occur in patients treated with 17-OHPC. However, in the indications of metrorrhagia and dysmenorrhoea, women are of childbearing age. As for the indications of amenorrhea and artificial cycles, a pregnancy in these women cannot be excluded because either pregnancy is the goal of the treatment or amenorrhea is effectively corrected and therefore allows for a pregnancy to occur. Therefore, the PRAC considered that 17-OHPC administration during or in close temporal relation to pregnancy can occur in these indications. Indeed, a pregnancy is possible in the days following 17-OHPC administration during the second part of the cycle. Considering the long half-life of 17-OHPC and that 17-OHPC is retrieved in foetal circulation up to 44 days after the last injection, embryo-foetal exposure can last for at least 1 month post 17-OHPC administration until the drug is fully eliminated. The PRAC also discussed the possibility of avoiding pregnancy during treatment. As 17-OHPC is a hormonal treatment, it is not possible to use a hormonal contraception since the combination of two hormonal treatments is not recommended either due to accumulation of metabolic/vascular risks or due to the risk of drug-drug interactions. Alternative options include the use of mechanical contraceptive methods such as copper intra-uterine devices (Cu IUDs). However, Cu IUDs are also not adequate for women with metrorrhagia or dysmenorrhoea as they enhance these symptoms. An

additional barrier method such as condoms is a less effective contraceptive method (85% versus 99% for Cu IUDs) and, even if complemented by regular pregnancy tests, these measures would not prevent exposure due to the long half-life of 17-OHPC. Therefore, these measures were not considered sufficient to prevent in utero exposure to 17-OHPC. Taking these into account and considering the absence of efficacy data, the Committee considered that the benefit-risk balance of 17-OHPC-containing medicinal products in the indications of 'juvenile and climacteric dysfunctional metrorrhagia' and 'disorders associated with progesterone deficiency (e.g. dysmenorrhoea, irregular menstrual periods, premenstrual syndrome, mastodynia)', 'primary and secondary amenorrhea' and 'artificial cycles in combination with an oestrogen' is negative.

Overall, the PRAC could not identify any measures that could effectively prevent in utero exposure to 17-OHPC in any of the authorised indications.

The PRAC concluded that the benefit-risk balance of 17-OHPC-containing medicinal products is no longer favourable in any indications. Consequently, the PRAC recommends the suspension of the marketing authorisations for 17-OHPC containing medicinal products.

For the suspension to be lifted the MAHs shall provide data demonstrating a positive benefit-risk balance in a defined patient population.

5. Summary of new activities and measures

The Committee, having considered the data submitted in the procedure was of the opinion that no risk minimisation measures could effectively prevent in utero exposure to 17-OHPC.

5.1. Pharmacovigilance activities

Periodic safety update reports (PSURs)

The submission of PSURs for 17-OHPC-containing medicinal products should be made in line with the requirements set up in a new entry in the European Union reference dates (EURD) list for 17-OHPC according to the international birth date (IBD) following a 3 year-frequency.

5.2. Direct Healthcare Professional Communications and Communication plan

The Committee agreed on the wording of a direct healthcare professional communication (DHPC) to inform healthcare professionals of the suspension of the marketing authorisation(s) of 17-OHPC-containing medicinal products in member states where 17-OHPC-containing medicinal products are authorised. The Committee also agreed on a communication plan.

6. Condition for lifting the suspension of the marketing authorisations

In order to lift the suspension of the marketing authorisations, the MAHs shall provide data demonstrating a positive benefit-risk balance in a defined patient population.

7. Grounds for recommendation

Whereas,

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data on hydroxyprogesterone caproate-containing medicinal products.
- The PRAC reviewed the totality of the data available for hydroxyprogesterone caproate-containing medicinal products in relation to the risk of cancer in offspring exposed to hydroxyprogesterone caproate in utero, as well as available efficacy data, and assessed their impact on the benefit-risk balance of those products. This included the responses submitted by the marketing authorisation holders in writing, the results of a pharmaco-epidemiological study by Murphy et al, 2022, data submitted during the review by its authors as well as the views expressed by an ad-hoc expert group.
- The PRAC considered that the results of this pharmaco-epidemiological study suggest an increased risk of cancer in offspring exposed to hydroxyprogesterone caproate in utero. This potential risk is of relevance in all therapeutic indications where an exposure in utero to hydroxyprogesterone caproate is possible. The Committee concluded that this risk is possible but cannot be confirmed due to study limitations.
- The PRAC considered the possibility of implementing risk minimisation measures but could not identify any measures that could effectively prevent in utero exposure to hydroxyprogesterone caproate.
- In addition, the PRAC considered the results of the PROLONG study and meta-analyses in the context of available data on efficacy of hydroxyprogesterone caproate-containing medicinal products in the prevention of premature parturition, and concluded that they showed no efficacy. Further, the PRAC noted that there is limited data of efficacy in other obstetrical and gynaecological indications for which hydroxyprogesterone caproate is authorised.

The Committee, as a consequence, considers that the benefit-risk balance of hydroxyprogesterone caproate-containing medicinal products is no longer favourable in all authorised indications.

Therefore, pursuant to Article 116 of Directive 2001/83/EC, the Committee recommends the suspension of the marketing authorisations for hydroxyprogesterone caproate-containing medicinal products.

The conditions imposed to lift the suspension of the marketing authorisations are set out in section 6 of this report.

References

Blackwell S.C., Gyamfi-Bannerman C., Biggio J.R., et al. 17-OHPC to prevent recurrent preterm birth in singleton gestations (PROLONG Study): A multicenter, international, randomized double-blind trial. Am J Perinatol. 2020, 37(2): 127-136 doi:10.1055/s-0039-3400227

Breuking S.H., De Ruigh A.A., Hermans F.J.R., et al. Progestogen maintenance therapy for prolongation of pregnancy after an episode of preterm labour: A systematic review and meta-analysis. BJOG. 2023 Oct;130(11):1306-1316. doi: 10.1111/1471-0528.17499. Epub 2023 Apr 19. PMID: 37077041

California Cancer Registry. Cancer reporting in California. 2021. Available at: https://www.ccrcal. org/submit-data/cancer-registrars-hospitals-andfacilities/reporting-by-cancer-registrars/. Accessed March 26, 2021

Care A., Nevitt S.J., Medley N., et al. Interventions to prevent spontaneous preterm birth in women with singleton pregnancy who are at high risk: systematic review and network meta-analysis BMJ 2022; 376 :e064547 doi:10.1136/bmj-2021-064547

Caritis S.N., Sharma S., Venkataramanan R., et al. Pharmacokinetics of 17-hydroxyprogesterone caproate in multifetal gestation. Am J Obstet Gynecol. 2011;205(1):40. e1–e8

Caritis S.N., Sharma S., Venkataramanan R., et al. Pharmacology and placental transport of 17-hydroxyprogesterone caproate in singleton gestation. Am J Obstet Gynecol. 2012;207(5):398. e1–e8

Chang C.Y., Nguyen C.P., Wesley B., et al. Withdrawing approval of Makena - A proposal from the FDA Center for Drug Evaluation and Research. N Engl J Med. 2020 Dec 10;383(24):e131. doi: 10.1056/NEJMp2031055. Epub 2020 Nov 3. PMID: 33140923

Devall A.J., Papadopoulou A., Podesek M., et al. Progestogens for preventing miscarriage: A network meta-analysis (Review). Cochrane Database Syst Rev, 2021, CD013792. doi: 10.1002/14651858.CD013792.pub2

Feghali M., Venkataramanan R., Caritis S. Prevention of preterm delivery with 17-hydroxyprogesterone caproate: pharmacologic considerations. Semin Perinatol, 2014, 38: 516-522

Ferrari F., Minozzi S., Basile L., et al. Progestogens for maintenance tocolysis in symptomatic women. A systematic review and meta-analysis. PLoS One. 2023 Feb 22;18(2):e0277563. doi: 10.1371/journal.pone.0277563. PMID: 36812243; PMCID: PMC9946203

Haas D.M., Hathaway T.J., Ramsey P.S. Progestogen for preventing miscarriage. Cochrane Database Syst Rev, 2019, CD003511

Killion J.A., Giddings B.M., Chen Y., et al. Cancer in California, 1998e2015. 2018. Available at: https://www.ccrcal.org/download/68/ special-reports-for-all-cancers/7639/cancer-incalifornia-1988-2015-2.pdf. Accessed March 26, 2021. 40

Meis P.J., Klebanoff M., Thom E., et.al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med, 2003, 348: 2379-2385

Murphy C.C., Cirillo P.M., Krigbaum N.Y., et al. In utero exposure to 17α-hydroxyprogesterone caproate and risk of cancer in offspring. Am J Obstet Gynecol. 2022; 226; 132.e1-14. doi:10.1016/j.ajog.2021.10.035

Nohr E.A., Liew Z. (2018). How to investigate and adjust for selection bias in cohort studies, Acta Obstetricia et Gynecologica Scandinavica, 97(4), pp. 407–416. Available at: https://doi.org/10.1111/aogs.13319

Romero R., Stanczyk F.Z. Progesterone is not the same as 17α-hydroxyprogesterone caproate: implications for obstetrical practice. Am J Obstet Gynecol. 2013 Jun;208(6):421-6. doi: 10.1016/j.ajog.2013.04.027. Epub 2013 Apr 30. PMID: 23643669; PMCID: PMC4120746

Saccone G., Schoen C., Franasiak J.M., et al (2017). Supplementation with progestogens in the first trimester of pregnancy to prevent miscarriage in women with unexplained recurrent miscarriage: a systematic review and meta-analysis of randomized, controlled trials, Fertility and Sterility, 107(2), pp. 430-438.e3. Available at: https://doi.org/10.1016/j.fertnstert.2016.10.031

Stewart L.A., Simmonds M., Duley L., et al. Evaluating progestogens for preventing preterm birth international collaborative (EPPPIC): meta-analysis of individual participant data from randomised controlled trials. Lancet 2021;397:1183–94

Vidaeff A.C., Belfort M.A. Critical appraisal of the efficacy, safety, and patient acceptability of hydroxyprogesterone caproate injection to reduce the risk of preterm birth. Patient Prefer Adherence. 2013 Jul 11;7:683-91. doi: 10.2147/PPA.S35612. PMID: 23874089; PMCID: PMC3714001

Wahabi H.A., Fayed A.A., Esmaeil S.A., et al. Progestogen for treating threatened miscarriage. Cochrane Database of Systematic Reviews, 2018(8). Available at: https://doi.org/10.1002/14651858.cd005943.pub5