Annex II

Scientific conclusions

Scientific conclusions

In November 2021, a pharmaco-epidemiological study by Murphy et al[1] 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[2], 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.

The PRAC adopted a recommendation on 16 May 2024 which was then considered by the CMDh, in accordance with Article 107k of Directive 2001/83/EC.

Overall summary of the scientific evaluation by the PRAC

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[3] 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

[1] 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
[2] 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
[3] 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

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[4]; Care et al, 2022[5]) 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.

[4] 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

[5] 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

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 dysmenorrhea 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 recommended 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.

Grounds for PRAC 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, considered 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 recommended the suspension of the marketing authorisations for hydroxyprogesterone caproate-containing medicinal products.

The condition imposed to lift the suspension of the marketing authorisation(s) is set out in Annex III as follows: the MAH(s) shall provide data demonstrating a positive benefit-risk balance in a defined patient population.

CMDh position

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

Overall conclusion

The CMDh, as a consequence, considers that the benefit-risk balance of hydroxyprogesterone caproate-containing medicinal products is not favourable.

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

For the suspension of hydroxyprogesterone caproate-containing medicinal products to be lifted, the MAH(s) shall provide data demonstrating a positive benefit-risk balance in a defined patient population.