17 July 2024

Suspension of the marketing authorisations of medicinal products containing hydroxyprogesterone caproate

Dear Healthcare professional,

The marketing authorisation holder(s) of medicinal products containing hydroxyprogesterone caproate in agreement with the European Medicines Agency would like to inform you of the following:

Summary

- **The results of a large epidemiological study suggest an increased risk of cancer in offspring exposed to 17-hydroxyprogesterone caproate (17-OHPC) in utero. This risk is possible but cannot be confirmed due to study limitations.**
- **A multicentre, double-blind randomised controlled trial has shown lack of efficacy of 17-OHPC in the prevention of preterm birth. There is limited data of efficacy in other obstetrical and gynaecological indications for which 17-OHPC is authorised.**
- **The benefit-risk balance of 17-OHPC-containing medicines is no longer considered positive in all indications and therefore the marketing authorisations of these medicines have been suspended in the European Union (EU).**
- **17-OHPC-containing medicines should no longer be prescribed or dispensed. Alternative treatment options should be considered for all indications.**

Background

Hydroxyprogesterone caproate is a synthetic progestogen authorised as an intramuscular injection to treat various gynaecological and obstetric conditions[1], with different pharmacological properties to natural progesterone.

In May 2023 an EU-wide review was initiated at the European Medicines Agency (EMA) to evaluate the benefit-risk balance of 17-OHPC in all its authorised indications. This followed concerns regarding the safety and efficacy of 17-OHPC, based on data from a pharmaco-epidemiological study[2] and a clinical trial[3], respectively.

In November 2021, results of a pharmaco-epidemiological study[2] conducted in the United States of America (U.S.A.) following a population-based cohort of > 18,000 individuals (of whom 234 individuals or about 1% were exposed *in utero* to 17-OHPC), for approximately 50 years from birth were published. This study suggested that *in utero* exposure to 17-OHPC may be associated with a higher risk of cancer in offspring exposed *in utero* as compared to non-exposed (adjusted HR 1.99, [95% CI 1.31, 3.02]). In

[1] 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; Risk of premature parturition associated with uterine hypermotility; protection of pregnancy in the event of surgery; disorders associated with progesterone deficiency (e.g. dysmenorrhoea, irregular menstrual periods, premenstrual syndrome, mastodynia); juvenile and climacteric dysfunctional metrorrhagia; sterility due to a luteal phase defect, luteal insufficiency; artificial cycles, in combination with an oestrogen; primary and secondary amenorrhea

[2] Murphy C.C., et al., In utero exposure to 17α-hydroxyprogesterone caproate and risk of cancer in offspring. Am J Obstet Gynecol. 2022, 226(1): 132.e1-132.-e14. doi:10.1016/j.ajog.2021.10.035

[3] 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. 2020, 37(2): 127-136 doi:10.1055/s-0039-3400227

absolute terms, the data suggest the estimated incidence of cancer is low among individuals exposed *in utero* (lower than 25/100,000 person-years). This risk is possible but cannot be confirmed due to study limitations. It was not possible to identify any measures to effectively prevent *in utero* exposure to 17-OHPC.

In 2020, results of a multicentre, double-blind randomised controlled clinical trial[3] also conducted in the U.S.A. between 2009 and 2018 showed that 17-OHPC is no more effective than placebo in preventing preterm birth in women with history of spontaneous preterm delivery or reducing serious events associated with prematurity in the newborns. Subsequent meta-analyses[4,5] were published confirming the absence of benefit of 17-OHPC in the prevention of preterm birth regardless of risk factors.

In view of the findings from the pharmaco-epidemiological study and given the results of the clinical trial and meta-analyses above as well as the limited data of efficacy in its other indications, the benefit-risk balance of 17-OHPC-containing medicines is no longer favourable in all authorised indications. Marketing authorisations for these medicines have been suspended and they will no longer be available.

17-OHPC-containing medicines should no longer be prescribed or dispensed. Alternative treatment options should be considered for all indication.

[4] Stewart LA, 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, Donegan S, Good L, Hampson L 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