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An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

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IMPORTANT MEDICINE SAFETY INFORMATION

APPROVED BY THE HPRA
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Health Products Regulatory Authority

17th July 2024

European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC) recommends suspension of the marketing authorisations of medicinal products containing 17-hydroxyprogesterone caproate

Dear Healthcare Professional,

The Health Products Regulatory Authority (HPRA) would like to inform you that the EMA's safety committee, PRAC, has recommended suspending the marketing authorisations of **medicinal products containing 17-hydroxyprogesterone caproate (17-OHPC)** across the European Union (EU).

These medicines are not authorised in Ireland, but are approved in certain other EU countries, including Austria, France, and Italy, under the trade names Proluton Depot, Progesterone Retard Pharlon, and Lentogest. This communication is issued as the HPRA has been notified of the supply of 17-OHPC containing medicines in Ireland as exempt medicinal products (sometimes referred to as 'unlicensed medicines') for individual patients under the direct personal responsibility of the practitioner.

Summary

- **The results of a large epidemiological study suggest an increased risk of cancer in offspring exposed to 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 EU.**

- **The PRAC has recommended that 17-OHPC containing medicines should no longer be prescribed or dispensed. Alternative treatment options should be considered for any indication.**
- **The outcome of this review does not affect the use of progesterone, which works in a different way to 17-OHPC.**

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 efficacy and safety of 17-OHPC, based on data from a clinical trial[2] and a pharmaco-epidemiological study,[3] respectively.

In November 2021, results of a pharmaco-epidemiological study[3] conducted in the 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 absolute terms, the data suggest the estimated incidence of cancer is low among individuals exposed in utero (lower than 25/100,000 persons-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[2] 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

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[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 (dysmenorrhoea, irregular menstrual periods, premenstrual syndrome, mastodynia, etc); 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] 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

[3] 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

serious events associated with prematurity in 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.

The PRAC however noted a low number of cancer cases in the study in the offspring exposed to 17-OHPC in utero, and that the study had limitations, such as the potential for confounding due to limited capture of information on risk factors for cancer. The PRAC therefore assessed that a risk of cancer is possible but is not confirmed.

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.

Call for reporting

Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, website: www.hpra.ie.

Yours sincerely,

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[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