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Hydroxyprogesterone caproate medicines to be suspended from the EU market

Review of studies raises possible safety concern and finds no effect in preventing premature birth

EMA's safety committee, PRAC, has recommended the suspension of the marketing authorisations for medicines containing 17-hydroxyprogesterone caproate (17-OHPC) in the European Union (EU). A review by the PRAC concluded that there is a possible but unconfirmed risk of cancer in people exposed to 17-OHPC in the womb. In addition, the review considered new studies which showed that 17-OHPC is not effective in preventing premature birth; there are also limited data on its effectiveness in other authorised uses.

In some EU countries, 17-OHPC medicines are authorised as injections to prevent pregnancy loss or premature birth in pregnant women. They are also authorised for the treatment of various gynaecological and fertility disorders, including disorders caused by a lack of a hormone called progesterone.

The PRAC reviewed the results from a large population-based study[1], which looked at the risk of cancer in people who had been exposed to 17-OHPC in the womb, over a period of about 50 years from the time they were born. Data from this study suggest that these people might have an increased risk of cancer compared with those who were not exposed to the medicines. However, the PRAC noted that there was a low number of cancer cases in the study and that the study had some limitations, such as limited information on risk factors for cancer. The Committee therefore concluded that the risk of cancer in people exposed to 17-OHPC in the womb is possible, but cannot be confirmed due to uncertainties.

In its review, the PRAC also considered data on the effectiveness of 17-OHPC medicines in their authorised uses, including the results from a study[2] looking at how well they prevented premature birth. The study, which involved over 1,700 pregnant women with a history of preterm delivery, found that 17-OHPC is no more effective than placebo (a dummy treatment) in preventing recurrent premature birth or medical complications due to prematurity in newborns. The Committee also

[1] Murphy CC, et al. In utero exposure to 17α-hydroxyprogesterone caproate and risk of cancer in offspring. Am J Obstet Gynecol. 2022 Jan;226(1):132.e1-132.e14 doi:10.1016/j.ajog.2021.10.035.
[2] Blackwell, SC, 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 Jan;37(2):127-136 doi:10.1055/s-0039-3400227.

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reviewed two published meta-analyses[3,4] (combined analyses of multiple studies), which confirmed that 17-OHPC is not effective at preventing preterm birth. For the other authorised uses of 17-OHPC, the PRAC concluded that there is limited evidence of effectiveness. During the review, input was also sought from experts in obstetrics, gynaecology and fertility treatment, and from patient representatives.

In view of the concern raised by the possible risk of cancer in people exposed to 17-OHPC in the womb, together with the data on the effectiveness of 17-OHPC in its authorised uses, the PRAC considered that the benefits of 17-OHPC do not outweigh its risks in any authorised use. The Committee is therefore recommending the suspension of the marketing authorisations for these medicines. Alternative treatment options are available.

Information for patients

- EMA is recommending that medicines containing 17-hydroxyprogesterone caproate (17-OHPC) are removed from the EU market. In some EU countries, these medicines were authorised to prevent pregnancy loss or premature birth in pregnant women and to treat certain gynaecological and fertility disorders.
- A review by EMA's safety committee, PRAC, found that there is a possible increased risk of cancer in people who have been exposed to 17-OHPC in the womb, although the number of cases remains low. The Committee concluded that this increased risk is possible but cannot be confirmed.
- The review also found that medicines containing 17-OHPC are not effective in preventing preterm delivery in pregnant women. In addition, there were limited data on the effectiveness of 17-OHPC medicines in other authorised uses.
- Given the data on the effectiveness of 17-OHPC in its authorised uses, together with the concern of a possible risk of cancer in people who were exposed to the medicine in the womb, the Agency is recommending that these medicines are removed from the market in the EU.
- Other treatment options are available. If you are using a medicine containing 17-OHPC, your doctor will discuss switching to a suitable alternative with you.
- The outcome of this review does not affect the use of progesterone, which works in a different way to 17-OHPC.
- If you have questions about your past or present treatment, please contact your healthcare provider.

Information for healthcare professionals

- EMA’s safety committee, PRAC, has recommended the suspension of medicines containing 17-hydroxyprogesterone caproate (17-OHPC) in the EU because the overall benefit-risk balance of these medicines is no longer considered positive.

[3] 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 doi:10.1016/S0140-6736(21)00217-8.
[4] 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.

- The results of a large epidemiological study suggest a possible increased risk of cancer in people exposed to 17-OHPC in the womb compared with those who were not exposed to the medicine (adjusted HR 1.99 [95% CI 1.31, 3.02]). In absolute terms, the data suggest that the estimated incidence of cancer is low among people exposed in the womb (less than 25/100,000 persons-years). The study has limitations and the possible risk cannot be confirmed.
- In terms of efficacy, data from a multicentre, double-blind randomised controlled trial have shown a lack of efficacy of 17-OHPC in the prevention of preterm birth; there are limited data on efficacy in other obstetric, gynaecological and fertility indications authorised in the EU.
- Healthcare professionals should no longer prescribe or dispense 17-OHPC medicines and should consider appropriate alternatives for any indication.
- The outcome of this review does not affect the use of progesterone, which works in a different way to 17-OHPC.
- A direct healthcare professional communication will be sent to relevant healthcare professionals in due course and published on a dedicated page on the EMA website.

More about the medicine

17-hydroxyprogesterone caproate (17-OHPC) is a synthetic form of hydroxyprogesterone which naturally occurs in the body and is formed from progesterone. Progesterone is involved in preparing the endometrium (womb lining) for pregnancy and maintaining it during pregnancy. 17-OHPC is thought to attach to receptors (targets) on cells that normally are targeted by progesterone. This was expected to reduce the risk of pregnancy loss or premature labour in pregnant women and help treat certain infertility and gynaecological disorders related to a lack of progesterone. 17-OHPC has different pharmacological properties to progesterone.

17-OHPC is available as a solution for injection. Within the EU, the medicine is currently authorised in Austria, France, and Italy under the trade names Proluton Depot, Progesterone Retard Pharlon and Lentogest.

More about the procedure

The review of 17-OHPC was initiated at the request of France, under Article 31 of Directive 2001/83/EC.

The review was carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which has issued a set of recommendations. As hydroxyprogesterone-containing medicines are all authorised nationally, the PRAC recommendations will be forwarded to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which will adopt its position. The CMDh is a body representing EU Member States as well as Iceland, Liechtenstein and Norway. It is responsible for ensuring harmonised safety standards for medicines authorised via national procedures across the EU.