SAFETY ALERT

DRAP SAFTEY ALERT NO. 58

Suspension of marketing authorisations of 17-Hydroxyprogesterone caproate (17-OHPC) due to its ineffectiveness in authorised uses.

Date: 1st of July, 2025.

Target Audience.

- Provincial Health Departments/Provincial PV Centres/Healthcare Commissions;
- Manufacturers and importers of 17-Hydroxyprogesterone Caproate (17-OHPC); and
- Healthcare Professionals.

Background.

The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) in May, 2024 recommended the suspension of the marketing authorisations for medicines containing 17-hydroxyprogesterone caproate (17-OHPC). The PRAC reviewed the results of a large population-based study, 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 PRAC 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. On 26 June 2024, the CMDh endorsed the recommendation from EMA's safety committee, PRAC, to suspend the marketing authorisations for medicines containing 17-hydroxyprogesterone caproate (17-OHPC) in the European Union (EU).

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 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 a placebo (a dummy treatment) in preventing recurrent premature birth or medical complications due to prematurity in newborns. The Committee also reviewed two published meta-analyses (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.

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 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 therefore recommended the suspension of the marketing authorisations for these medicines. Alternative treatment options are available.

Previously, the US-FDA, in April 2023 announced the final decision to withdraw approval of Makena (Hydroxyprogesterone caproate)—a drug that had been approved under the accelerated approval pathway. This drug was approved to reduce the risk of preterm birth in women pregnant with one baby who has a history of spontaneous preterm birth. The decision was issued jointly by the FDA Commissioner and Chief Scientist. The FDA approved Makena (Hydroxyprogesterone caproate)— under the accelerated approval pathway in 2011 based on a determination that the sponsor had demonstrated a drug effect on an intermediate clinical endpoint that was reasonably likely to predict clinical benefit. The agency's approval included a requirement that the sponsor conduct a post-marketing confirmatory study. The ensuing confirmatory study did not verify clinical benefit and the FDA's Center for Drug Evaluation and Research (CDER) proposed withdrawing the drug's approval in 2020. The sponsor requested a hearing, which was held in October 2022. Following the hearing, the FDA Commissioner and Chief Scientist reviewed the record for this matter, including the submissions by CDER and sponsor Covis Pharma, public comments to the docket, the transcript of the hearing and the Presiding Officer's report. Based on that review, they have decided to withdraw approval of Makena and generic versions of Makena. Approvals of these drugs have been withdrawn because the drugs are no longer shown to be effective and the benefits do not outweigh the risks for the indication for which they were approved.

Action in Pakistan.

The case was discussed in the 5th meeting of the Pharmacovigilance Risk Assessment Expert Committee (PRAEC) held on 2nd of Janauary, 2025 which decided as per Rule 10 (1) (h) (v) of the Pharmacovigilance Rules, 2022 to suspend the 17-hydroxyprogesterone caproate (17-OHPC) in Pakistan due to risk of cancer in people exposed to 17-OHPC in the womb together with its effectiveness in its authorised uses wherein benefits of 17-OHPC do not outweigh its risks in any authorised use. As per Rule 10 (1) (e) of the said rules and based on the benefit-risk assessment, the PRAEC recommended to the Registration Board for the suspension of registration of 17-OHPC containing medicine in Pakistan. Accordinlgy, the Registration Board in its 346th meeting held on 22nd April, 2025, suspended the registration of 17-OHPC containing medicine in Pakistan.

Therapeutic Good Affected.

Name: 17-hydroxyprogesterone caproate (OHPC) is a synthetic progesterone (a steroid hormone that acts like progesterone). 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 progesterone.

Advice for Healthcare Professionals.

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 this medicine. 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. Therefore, based on the benefit-risk assessment, the PRAEC-DRAP recommended the suspension of medicines containing 17-hydroxyprogesterone caproate (17-OHPC) to the Registration Board. Accordinlgy, the Registration Board, in its 346th meeting, suspended registration of 17-OHPC medicines in Pakistan. Healthcare professionals should no longer prescribe or dispense these 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.

Advice for patients.

Patients are informed that DRAP has decided to suspend the registration of 17-Hydroxyprogesterone Caproate in Pakistan; therefore, patients should stop using these products, and discuss with their doctors for other treatment options which are available for their disease condition. Patients are also advised not to confuse the Hydroxyprogesterone caproate (17-OHPC) with progesterone, which works in a different way to 17-OHPC.

Guidelines for reporting Adverse Drug Reactions (ADRs).

Healthcare professionals and patients are requested to report any adverse drug reaction with 17-Hydroxyprogesterone caproate (17-OHPC) and/or any other medicine to the National Pharmacovigilance Centre (NPC), Drug Regulatory Authority of Pakistan (DRAP) through the Med Vigilance E-Reporting System (E-forms) available on the DRAP website. Similarly, ADRs can also be reported through the VigiMobile App, which can be downloaded by scanning the barcode available on the DRAP website.

References.

- Minutes of the 5th meeting of the Pharmacovigilance Risk Assessment Expert Committee (PRAEC), DRAP.
- EMA: Hydroxyprogesterone caproate-containing medicinal products - referral.
- US-FDA Decision to Withdraw Approval of Makena