12 May 2023
EMA/PRAC/194264/2023

PRAC List of questions

To be addressed by the marketing authorisation holder(s) for hydroxyprogesterone-containing medicinal products

Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure number: EMEA/H/A-31/1528

INN/active substance: hydroxyprogesterone

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Questions

The marketing authorisation holders (MAHs) are requested to address the following questions:

Question 1

Concerning your hydroxyprogesterone-containing medicinal product(s), please complete the annexed tables with:

a. Information on the marketing status, cumulative sales and patient exposure data since the first marketing authorisation, stratified by EU Member States and indication.

b. An overview of the approved therapeutic indication(s) (section 4.1), posology and method of administration (section 4.2), contraindications (section 4.3), special warnings and precautions for use (section 4.4), fertility, pregnancy and lactation (section 4.6) and undesirable effects (section 4.8) included in the summary of products characteristics (SmPC), and corresponding text from the package leaflet (PL) regarding the risk of use during pregnancy. Main differences between SmPCs/PLs in the different EU Member States should be tabulated.

Question 2

Please provide a review of all available non-clinical evidence on hydroxyprogesterone caproate from sponsored/non-sponsored studies or any source (e.g. literature) in relation to i*n vitro/in vivo* genotoxicity, repeat dose toxicity, carcinogenicity, developmental and reproductive toxicity. Exposure margins for any relevant non-neoplastic and neoplastic findings should be provided. In addition, a discussion on the clinical relevance of the non-clinical findings should be included.

Question 3

a. Provide a cumulative review from the literature and other available safety data from any source relevant to the risk of cancer in offspring exposed *in utero* to hydroxyprogesterone caproate with a particular focus on the recently published study by Murphy et al[1]. This should include any relevant information covering, when available, the trimester of pregnancy or gestational age at the time of exposure, mother's medical history, indication, cumulative administered dose, number of injections, duration of treatment and time to onset of the event under evaluation. Moreover, discuss the absolute risk and expected incidence of cancer in the offspring after *in utero* exposure to hydroxyprogesterone caproate, as well as the magnitude of the increased risk with exposure as compared to non-exposed.

b. Based on the pharmacodynamic and pharmacokinetic properties of hydroxyprogesterone caproate, provide a discussion on the possible underlying mechanism leading to cancer development in offspring after *in utero* exposure to hydroxyprogesterone.

Question 4

Please provide a full appraisal of the efficacy data in support of the obstetrical and gynaecological indications. The discussion should encompass a critical analysis of the results of the PROLONG study[2].

[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, 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 Jan;37(2):127-136. doi:10.1055/s-0039-3400227

A summary of clinical guidelines in relation to hydroxyprogesterone caproate use in the EU approved indications should also be provided and discussed.

Question 5

Please propose risk minimisations measure(s) to address any change(s) to the benefit-risk balance of your medicinal product(s), including changes to the product information and/or any further risk minimisation measure(s). Activities to assess their effectiveness should also be proposed.

Question 6

In view of the responses to the questions above, please provide a benefit-risk assessment of hydroxyprogesterone-containing medicinal product(s) for each of the currently approved indications in the EU.

Annex

Question 1

a.

Substance name/INN	Product name	Member State	Type of marketing authorisation	Marketing and legal status	Indications[1]	Pharmaceutical forms and strengths	Sales figures	Estimated patient exposure[2]	Doses (in clinical practice)	Treatment duration (in clinical practice)

[1]. MAH should clearly indicate for which country a specifically dedicated presentation has been granted for a particular indication.
[2]. Expressed as number of exposed patients and stratified by EU Member State and by indication. Reasonable efforts should be made to obtain this information; potential sources in addition to sales data include registries and healthcare databases. If no precise data is available an estimate can be provided.

b.

Product Information	SmPC	PL	Main differences in SmPCs/PLs between the different EU Member States
Per indication[3]			
Posology (incl. max. daily dose)			
Contraindications			
Warnings and precautions			
Fertility, pregnancy and lactation			
Undesirable effects			

[3]. MAH should clearly indicate the approved indication in the cell and replicate the table for each authorised indication.