EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 March 2020
EMA/PRAC/121855/2020

PRAC List of questions

To be addressed by the marketing authorisation holder(s) for ulipristal acetate 5mg medicinal products

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

Procedure number: EMEA/H/A-31/1496

Esmya EMEA/H/A-31/1496/C/2041/0049

Ulipristal Acetate Gedeon Richter EMEA/H/A-31/1496/C/5017/0002

INN/active substance: ulipristal acetate

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1. Background

Ulipristal acetate is an orally active synthetic selective progesterone receptor modulator (SPRM), characterised by a tissue-specific partial progesterone antagonist effect in the target tissues (uterus, cervix, ovaries, hypothalamus). The 5mg tablet form is currently approved in the EU for the following indications:

- one treatment course of pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.
- intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age who are not eligible for surgery.

The treatment consists of 5 mg daily for treatment courses of up to 3 months each.

In May 2018, PRAC finalised a review of the benefit-risk balance of Esmya under Article 20 of Regulation (EC) No 726/2004 initiated due to three cases of serious liver injury leading to liver transplantation (a fourth case was reported during the review), and recommended as an outcome of this procedure:

- The indications to be restricted to only one treatment course of pre-operative treatment and for intermittent treatment to adult women of reproductive age who are not eligible for surgery;
- A contraindication in patients with underlying hepatic disorder;
- Liver tests to be conducted before, during and after the first two treatment courses;
- Esmya to be discontinued in case of elevated transaminases or symptoms compatible with liver injury.

In December 2019, EMA was informed of a new case of serious liver injury leading to liver transplantation following exposure to Esmya (5^{th} case). Based on the report, this case further supports the causal association between Esmya and serious liver injury.

This new case raises concerns as, despite adherence to the implemented risk minimisation measures, the progression in the development of hepatic failure leading to liver transplantation, could not be prevented.

The seriousness of the case reported, the causal relationship between ulipristal acetate 5mg and acute liver failure, and its occurrence despite adherence to risk minimisation measures are considered of major concern and would warrant an in-depth investigation of the case and its impact on the benefit-risk balance of ulipristal acetate 5 mg and further consideration of the effectiveness of the implemented risk minimisation measures.

On 5 March 2020, the European Commission (EC) initiated a procedure under Article 31 of Directive 2001/83/EC and requested the Agency to assess the above concerns and their impact on the benefit-risk balance of ulipristal acetate 5mg. The EC requested the Agency to give its opinion, on whether the marketing authorisation for ulipristal acetate should be maintained, varied, suspended or revoked and as to whether provisional measures are necessary pending the outcome of the scientific review.

2. Questions

The marketing authorisation holders of ulipristal acetate 5mg are requested to address the following questions:

Question 1

Please provide in the annexed table, information on current marketing status for ulipristal 5 mg worldwide and within the EU member states.

a) Number of ongoing clinical studies, the indication to be studied, in which countries they are performed, and the number of patients involved.

b) Figures on sales and patient exposure data worldwide stratified per six-monthly intervals for the post-referral period and per EU member state from the date of first launch in the EU up to 28 February 2018 (data cut-off for the Art 20 procedure in 2018) and from 28 February 2018 up to now, as well as data on the use in clinical practice in the EU including information on dose, duration of treatment, number of treatment courses, number of patients starting ulipristal acetate 5 mg treatment with the intention to undergo surgery for uterine fibroids and the number of patients who *de facto* underwent surgery (from 28 February 2018 up to now). Also specify the percentage of myomectomy and hysterectomy and the rate of patients initially candidates to hysterectomy and that was reverted to conservative surgery (myomectomy).

c) An overview of the approved indication(s) of ulipristal acetate 5mg outside the EU.

Question 2

The MAH of Esmya should address this question:

For the new case of serious liver injury leading to liver transplantation, causality was assessed as probable/highly probable by the MAH. However, at 6 weeks after Esmya treatment discontinuation CMV IgM and IgG were tested positive, but negative for DNA-CMV, suggesting either a de novo or reactivation of a CMV infection. The MAH should provide a more in-depth discussion on causality, taking any potential confounding factors or other aetiologies into consideration and explain how these impacts causality assessment. The MAH is encouraged to obtain any further clinical information that may contribute to a more detailed causality assessment, e.g. any medications administered/ prescribed from date of Esmya discontinuation and subsequent hospitalisation, laboratory tests for CMV before 6 weeks of Esmya discontinuation and data regarding pathology in the explanted liver.

Question 3

Please provide a review of all cases of serious liver toxicity reported post marketing. Cases occurring before and after the data cut off for cases reviewed with in the previous referral should be presented separately. If new data have become available for cases presented in the previous review, this should be clearly indicated. For this purpose, all the MedDRA Preferred Terms (PTs) within the SMQ 'Hepatic disorders' (broad) as well as PT 'Liver transplantation', reported where ulipristal acetate is a suspected or interacting medicinal product should be provided. Please provide a summary of these cases in a tabular format as follows:

Case ID	Age (yrs)	Reported PT	Time to onset	Medical history	Concomitant medication*	Case description	Causality assessment

*including any hormonal contraceptive use, OTC medication or herbal products

For these cases, including those submitted in previous reviews, please present full case details (including CIOMS reports).

This should include reversibility of injury after ulipristal acetate 5 mg is withdrawn, explant histology for cases resulting in liver transplantation, laboratory results, and in addition to liver tests, also blood count including platelet values and if available, biomarkers such as phosphatidylethanol. Furthermore, pattern of liver injury and treatment discontinuation due to increase of liver enzymes should be described if available

Based on this material, please provide a causality assessment for serious cases of hepatic toxicity based on the information outlined in the table above. Possible risk factors should be discussed.

Question 4

Please provide a comprehensive review and discussion on the effectiveness of the risk minimisation measures (RMMs) for liver monitoring and in relation to patients with risk factors as detailed in sections 4.3 and 4.4 of the SmPC based on cases with elevated ALT/AST levels. Case presentation should be presented in a tabulated format. The discussion of effectiveness of RMMs should address at least the following aspects:

- Discuss the de-challenge information (positive or negative) relative to the causality assessment in each of the cases, taking into account any confounding factors or other aetiologies. If applicable, the same should done for re-challenge information.
- Discuss to what extent RMMs have been adhered to in the respective cases.
- Discuss the effectiveness of RMMs taken all the above into consideration.

Question 5

Based on the review undertaken, please discuss the need and feasibility for any further risk minimisation measures to mitigate the risk of serious liver toxicity, including changes to the product information, as well as proposals to monitor their effectiveness. Please also discuss communication activities (e.g. DHPC), as appropriate.

Question 6

Please provide an in-depth review of the benefits and risks of ulipristal acetate 5 mg for the treatment of uterine fibroids separately for each of the indications, with focus on the hepatic failure and effectiveness of RMMs, taking the data within the current review into account.

Annex

Question 1

INN	Product name	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 in patient years and stratified by Member State, by indication and by age (<12 and 12-18). 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.