30 November 2017
EMA/PRAC/791195/2017

PRAC List of questions

To be addressed by the marketing authorisation holder

Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data

Procedure No: EMEA/H/A-20/1460/C/2041/0043

Invented name: Esmya

INN/active substance: ulipristal acetate

Marketing authorisation holder: Gedeon Richter Plc.

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The marketing authorisation holder is requested to address the following questions:

Question 1

Please provide in an annexed table:

1. Information on current marketing status for ulipristal 5 mg (Esmya) worldwide and within the EU member states.
2. Number of clinical studies ongoing and number of patients involved.
3. Figures on sales and patient exposure data worldwide stratified per year and per EU member state from the date of first launch in the EU up to now, as wells data on the use in clinical practice including information on dose, duration of treatment, number of treatment courses, and concomitant treatment (characterisation of users, prescriptions…).
4. An overview of the approved indication(s) of Esmya outside the EU.

Question 2

Please provide available safety data relevant to evaluate the potential risk of hepatic failure with Esmya and an analysis of these data in its approved indications. This should include all relevant data sources including a short summary of data in relation to hepatic toxicity in non-clinical studies, clinical trials, pharmacoepidemiological studies and the literature.

Furthermore, a cumulative review of all cases (serious and non-serious) reported post marketing should be provided. For this purpose, all the MedDRA Preferred Terms (PTs) within the SMQ 'Hepatic disorders' (broad) as well as PT 'Liver transplantation', reported where ulipristal 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 serious cases, including those submitted in previous reviews, please submit all available information, to facilitate causality assessment.

This should include reversibility of injury after Esmya is withdrawn, explant histology for cases resulting in liver transplantation, laboratory results, and in addition to liver tests, also blood count including platelet values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 based on the information outlined in the table above. Possible risk factors should be discussed.

An overall critical assessment whether drug-induced liver injury is a risk for ulipristal 5 mg should be provided.

Question 3

Please provide a comprehensive review and discussion of potential mechanisms in relation to whether ulipristal 5 mg may be involved in the development of drug-induced liver injury. The following points should specifically be addressed, but other aspects should also be commented, as appropriate.

- The role of the dose, including cumulative dose, or chemical structure for suspecting ulipristal causing liver injury.
- Discuss the possibility whether liver injury may be a class effect of progesterone receptor modulators considering the effects noted with high dose of telapristone, based on currently available public literature, with special focus on mifepristone, the only other PRM currently in clinical use.
- Discuss, based on data, the role of the progesterone pathway in hepatic function, and whether alterations of this pathway, including by the mechanism of action of ulipristal, may affect an ongoing hepatic disorder.
- Comment on the possibility that Esmya treatment may have been initiated due to overlapping symptoms from underlying hepatic disorder.

Question 4

Please provide an overview of the literature regarding data on background incidence for acute liver failure and drug induced liver injury, with particular focus on Europe.

Question 5

Based on the review undertaken, please discuss the need and feasibility for risk minimization measures addressing hepatic safety, including changes of the product information, as well as the monitoring of 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 5 mg for the treatment of uterine fibrosis, with focus on the currently important potential risk for drug induced liver injury, 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.