Ref. Ares(2017)5862846 - 30/11/2017

NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 20 OF REGULATION (EC) 726/2004
E-mail: ReferralNotifications@ema.europa.eu

This notification is a referral under Article 20 of Regulation (EC) 726/2004 to the Pharmacovigilance Risk Assessment Committee (PRAC) made by the European Commission (EC):

Product(s) Name(s)	Esmya
Active substance(s)	Ulipristal acetate
Pharmaceutical form(s)	Tablets
Strength(s)	5 mg
Route(s) of Administration	Oral use
Marketing Authorisation Holder(s)	Gedeon Richter Plc

Esmya (Ulipristal acetate) is an orally-active synthetic selective progesterone receptor modulator (SPRM). Esmya is a centrally authorised product indicated for pre-operative treatment as well as intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. The treatment consists of 5 mg daily for treatment courses of up to 3 months each.

On 22 September 2017, a case of fulminant hepatitis leading to a hepatic transplantation in a patient treated with Esmya for uterine fibroids was reported to the French medicines agency (ANSM). A search for cases of hepatic disorders reported after the data lock point for the most recent periodic safety update report (PSUSA data lock point 22 February 2017) until 24 September 2017 was performed in Eudravigilance. This search retrieved two other cases of hepatitis resulting in liver transplantation, as well as other cases of hepatic disorders.

As an outcome of the evaluation of the above mentioned PSUSA procedure for Esmya covering the period of 23 February 2016 to 22 February 2017, the marketing authorisation holder was requested to submit a cumulative review of the important potential risk "Drug induced liver injury" as reflected in the Esmya Risk Management Plan, covering all relevant data sources including clinical studies, literature and post marketing reporting. The requested cumulative review was submitted in November 2017.

Overall, the post-marketing exposure to Esmya is estimated to be approximately 600,000 patients. Although the duration of exposure is uncertain for the post marketing experience, a mean duration of 3 months is considered a reasonable assumption. Thus, the reported patient exposure is estimated to correspond to 150,000 patient years. This results in 4 cases of serious hepatic injury being reported among 150,000 patient years of exposure. Acknowledging the uncertainty regarding background incidence and the information in the reported cases, the PRAC is of the view that the reported cases with an at least possible causal relationship with Esmya raise concern.

The seriousness of the reactions reported and the possible causal relationship between Esmya and acute liver failure, means an in-depth investigation of this risk and its impact on the benefit-risk balance of Esmya is warranted.

Medicinal product no longer authorised

In view of the above, the European Commission (EC) initiates a procedure under Article 20 of Regulation (EC) No 726/2004 and requests the Agency to assess the above concerns and their impact on the benefit risk balance of the centrally authorised medicinal product Esmya. The EC requests the Agency to give its opinion as soon as possible, and at latest by 31 May 2018, on whether the marketing authorisation for Esmya (ulipristal) should be maintained, varied, suspended or revoked.

As the request results from the evaluation of data resulting from pharmacovigilance activities, the opinion should be adopted by the Committee for Medicinal Products for Human Use on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee.

[redacted]

Signed

29/11/2017

Date

Olga Solomon
Head of Medicines: policy, authorisation and monitoring
Health and Food Safety Directorate General

Medicinal product no longer authorised

[redacted] Electronically signed on 29/11/2017 19:40 (UTC+01) in accordance with article 4.2 (Validity of electronic documents) of Commission Decision 2004/563