NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF REGULATION (EC) 726/2004

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This notification is a referral under Article 31 of Directive 2001/83/EC to the Pharmacovigilance Risk Assessment Committee (PRAC) made by the European Commission (EC):

Product name/Procedure name	Esmya, Ulipristal Acetate Gedeon Richter and generics
Active substance	Ulipristal acetate
Pharmaceutical form(s)	Tablets
Strength(s)	5 mg
Route(s) of Administration	Oral use
Gedeon Richter Plc	Gedeon Richter Plc, various

Ulipristal acetate is an orally active synthetic selective progesterone receptor modulator (SPRM). The 5mg tablet form is currently approved in the EU for the following indications:

- *Ulipristal acetate is indicated for one treatment course of pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.*
- *Ulipristal acetate is indicated for 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, the Pharmacovigilance Risk Assessment Committee (PRAC) finalised a review of the benefit-risk balance of Esmya (ulipristal acetate) under Article 20 of Regulation (EC) No 726/2004 initiated due to three cases of serious liver injury leading to liver transplantation, 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, the European Medicines Agency (EMA) was informed of a new case of serious liver injury leading to liver transplantation following exposure to Esmya. 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 5 mg tablet and acute liver failure, and its occurrence despite adherence to risk minimisation measures are considered of major concern. An in-depth investigation of the impact of this new case on the benefit-risk balance of ulipristal acetate 5 mg tablet, and further consideration of the effectiveness of the implemented risk minimisation measures is warranted.

In view of the above and the necessity to take an action at EU level, the European Commission (EC) considers that it is in the interest of the Union to refer the matter to the Agency and initiates a procedure under Article 31 of Directive 2001/83/EC and requests the Agency to assess the available evidence related to the above concerns and the impact on the benefit-risk balance of ulipristal acetate 5 mg tablet medicinal products.

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.

The EC requests the Agency to give its opinion as soon as possible and at the latest by 30 September 2020 on whether the marketing authorisation for these products should be maintained, varied, suspended or revoked.

In addition, the EC requests the Agency to give its opinion as soon as possible, as to whether provisional measures are necessary to ensure the safe and effective use of these medicinal products.

[redacted]

Signed Date 05.05.2020

Olga Solomon
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