

Background and recap of events leading up to current PRAC report

- In May 2018, PRAC finalised a review of the benefit-risk balance of Ulipristal Acetate (Esmya™) under Article 20 of Regulation (EC) No 726/2004, due to three cases of serious liver injury leading to liver transplantation. An additional case was reported regarding an acute liver failure associated with the use of Ulipristal Acetate 5mg during the review. At its conclusion, PRAC recommended the following measures to minimize the risk of serious liver injury associated with Ulipristal Acetate 5mg:
 - Restriction of indications 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;
 - Ulipristal Acetate (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 Ulipristal Acetate (5th case cumulatively). This new case raised concerns as, despite adherence to the implemented risk minimization measures, the progression in the development of hepatic failure leading to liver transplantation, could not be prevented.

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

- On March 12, 2020, the PRAC recommended suspension of the marketing authorisations of 5-mg Ulipristal Acetate (Esmya™ and generic medicines) while the review was ongoing. The European Commission issued a legally binding decision to suspend the marketing authorisation on 25 March 2020. The announcement stated:
 - EMA's safety committee (PRAC) recommended women to stop taking 5-mg ulipristal acetate (Esmya™ and generic medicines) for uterine fibroids while a safety review is ongoing.
 - This review started at the request of the European Commission following a recent case of liver injury, which led to liver transplantation in a patient taking the medicine.
 - In addition to existing patients, no new patients should start treatment with Ulipristal Acetate (Esmya™) 5mg ,
 - A 2018 EMA review concluded that there is a risk of rare but serious liver injury with Ulipristal Acetate medicines for the treatment of uterine fibroids, and measures were implemented to minimise the risk. However, as the new case

of serious liver injury occurred despite adherence to these measures, EMA is starting a new review.

- On September 4, 2020; PRAC issued its final review that 5-mg Ulipristal Acetate (Esmya™ and generic medicines) used for the treatment of symptoms of uterine fibroids can cause liver injury, including the need for liver transplantation. The PRAC has therefore recommended the revocation of the marketing authorisations of these medicines.

The PRAC recommendations will now be forwarded to the Committee for Medicinal Products for Human Use (CHMP), which will adopt an opinion, and the final stage involves the adoption of a legally binding decision by the European Commission, applicable in all EU Member States. The final stage of the review procedure is the adoption by the EC of a legally binding decision applicable in all EU Member States.