

concerns symptomatic treatment, PRAC concluded in March 2020 (i.e. at the start of this Article 31 referral procedure) that this new case had an impact on the benefit-risk balance of ulipristal acetate 5mg and that temporary measures were needed to protect public health during the review. As no measures that would sufficiently mitigate the risk of serious liver disorders in all patients treated with ulipristal acetate 5mg could be identified at that stage, the PRAC recommended on 12 March 2020 that the use of ulipristal acetate 5mg should be temporarily suspended while a thorough assessment of all available data related to the benefit-risk balance of ulipristal acetate 5mg and effectiveness of the risk minimisation measures be performed.⁴

4.1.1. Safety aspects

4.1.1.1. Acute liver failure and drug-induced liver injury with ulipristal acetate 5mg

Firm conclusions on the background incidence of drug-induced liver injury (DILI) and acute liver failure (ALF) in the general population in the EU cannot be drawn. This is due to the differences between the studies investigating the incidence of ALF secondary to DILI, among others, the diagnostic criteria applied, the severity of the disease, in- or exclusion of cases with acetaminophen, the type of patients collected, the variety in age groups and the fact that such studies were performed in only a limited number of countries in the EU. Generally, the outcome of an acute hepatic failure is unpredictable and is associated with high morbidity and mortality although overall survival has improved in past decades through advancements in intensive care management and emergency liver transplantation.

The risk of serious liver injury with ulipristal acetate 5mg was assessed in the context of the Article 20 review of Esmya and it was concluded by the PRAC that the product may carry a risk for serious liver injury. While uncertainties around causality remained, PRAC recognised the very serious outcome of the reported cases of liver injury.

Prior to the Article 20 review of Esmya (cut-off date: 28 February 2018), 105 cases had been reported within the Hepatic disorder SMQ, including 33 cases with serious liver disorder SMQ. Among 33 cases, 16 cases were reported with sufficient/partially sufficient information for causality assessment, including 4 cases of acute liver failure leading to liver transplantation. For these 4 cases, reviewed during the Article 20 procedure⁵, the causal association between Esmya and serious liver injury was assessed as possible or probable with remaining uncertainty regarding pre-existing liver disease in 2 cases, the role of Human Herpesvirus 6 infection in the third case and a possible role of hepatitis E infection in the fourth case. Generally, the peak time to onset of liver injury was around 140 days and the vast majority of the reported potential drug induced liver injuries occurred between 1 and 8 months (2 treatment cycles including 2 months pause).

As outcome of the Article 20 review of Esmya in 2018, the PRAC requested the MAH to perform *in-vitro* mechanistic studies to further explore potential links between ulipristal and drug induced liver injuries. A series of *in vitro* experiments in HepG2 cells were conducted to determine the potential of ulipristal (UPA) or its metabolite PGL4002 to elicit hepatotoxicity via known direct toxicological mechanisms, including oxidative stress/reactive metabolites, mitochondrial dysfunction, and disruption of bile salt homeostasis. The PRAC also requested the MAH to perform an *in-vitro* study on inhibition of transporter proteins.

None of these studies however could suggest that ulipristal acetate might inhibit efflux transporters BSEP, MRP2, MRP3, MRP4, cause mitochondrial dysfunction or oxidative stress or cytotoxicity at clinically relevant concentrations. These data, that were submitted and reviewed by the PRAC prior to

⁴ More information is available in the published [assessment report on provisional measures](#)

⁵ More information is available in the published [assessment report on the Article 20 review for Esmya](#)

