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SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

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

Invented name: Esmya

INN/active substance: ulipristal acetate

Procedure number: EMEA/H/A-20/1460/C/2041/0043

Note:

Assessment report as adopted by the PRAC and considered by the CHMP with all information of a commercially confidential nature deleted.



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1. Information on the procedure

Three cases of serious liver injury leading to a hepatic transplantation were reported between the marketing authorisation of Esmya (ulipristal acetate) and November 2017. In addition, other cases of hepatic injury were also reported post marketing for Esmya. Given the estimated exposure to Esmya of approximately 200,000 to 275,000 patient-years, the number of cases of serious liver injury leading to liver transplantation appears higher than expected, although background incidence on drug induced liver injury is uncertain. No information on hepatic events was at that time included in the Product Information of Esmya. Acknowledging the uncertainty regarding background incidence and the information in the reported cases, the seriousness of the reported cases raises concern. Since a possible causal relationship between Esmya and acute liver failure could not be ruled out, these cases prompted an in-depth investigation of this risk and its impact on the benefit risk balance of Esmya.

On 30 November 2017, the European Commission triggered a procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data, and requested the PRAC to assess the impact of the above concerns on the benefit-risk balance of Esmya and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

2. Scientific discussion

2.1. Introduction

Ulipristal acetate is an orally-active synthetic selective progesterone receptor modulator (SPRM), characterised by a tissue-specific partial progesterone antagonist effect in the target tissues (uterus, cervix, ovaries, hypothalamus). Esmya is a centrally authorised product available as tablets containing 5 mg of ulipristal acetate. It is 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 one tablet to be taken once daily for treatment courses of up to 3 months each. Repeated intermittent treatment has been studied up to 4 intermittent courses, and in a limited number of women data from up to 8 courses are available.

Uterine fibroids (uterine leiomyoma) are benign, monoclonal, hormone-sensitive, smooth muscle tumours of the uterus in premenopausal women. They are the most common tumour of the female reproductive tract in pre-menopausal women and have been reported to affect 20-40% of women during their reproductive years. Uterine fibroids are often asymptomatic; however, when they are symptomatic, the primary symptoms are heavy fibroid-related bleeding and subsequent anaemia, abdominal pressure and abdominal pain, increased urinary frequency and infertility related to the volume and location of the tumour. Uterine fibroids are commonly treated surgically through hysterectomy. Other, less invasive surgical treatment procedures include myomectomy, which may preserve fertility, uterine artery embolization and endometrial ablation, in case the dominant symptom is bleeding. However, surgery may not be a suitable option for all patients, due to its associated risks and potential impact on fertility. Alternative to surgery, medical treatment options currently approved for uterine fibroids are gonadotropin releasing hormone (GnRH) agonists and Esmya. GnRH agonists are effective in reducing fibroid-related bleeding, reducing abdominal symptoms and fibroid and uterine volume. Their use duration is however limited to 3 to 6 months due to side effects (hot flushes and increasing the risk of osteoporosis). Therefore, Esmya is the only long-term pharmacological treatment for moderate to severe symptoms of uterine fibroids currently approved.

Esmya was first authorised in the European Union on 23 February 2012. The post-marketing exposure to Esmya is estimated to be at around 765,000 patients (cut-off date: 28 February 2018). Assuming a

mean duration of 3 months, this corresponds to an exposure of approximately 200,000 to 275,000 patient-years.

Esmya is marketed in all European Union (EU) Member States, in Norway and Iceland. The largest use until November 2017 was in France, Germany and Spain, followed closely by Italy.

In December 2017, 12 studies were ongoing with Esmya 5 mg tablets. One (the PGL 14-001 “PREMIUM” study) is a non-interventional study intended to assess safety of Esmya in clinical practice, which aims at recruiting 1,500 patients. All other studies are small, either interventional or non-interventional, with up to 100 patients per study. Most of these studies are in patients with uterine fibroids, while some studies are in patients with adenomyosis, premenstrual dysphoric disorder, as well as a non-interventional study aimed at assessing changes in the mammary gland.

From February 2012 to November 2017, 51 cases of hepatic impairment associated with the use of Esmya were reported, of which 17 were serious and 34 were non serious. These correspond to a total of 68 Adverse Event (AEs), of which 24 were serious. Among those cases, three cases of acute liver failure leading to liver transplantation were identified. In view of the fact that the involvement Esmya in the development of acute liver failure was possible, and considering the seriousness of the reported cases, a review under Article 20 of Regulation (EC) No 726/2004 was initiated on 30 November 2017 to assess the potential risk of liver injury and its impact on the benefit-risk balance of the medicinal product. At the end of January 2018, another case of hepatic liver failure leading to transplantation was reported.

In light of this new case, and considering the cases reported before the initiation of the referral, a preliminary assessment of the available data was performed in February 2018. Based on this review, the PRAC considered that provisional measures were needed while the issue was being further reviewed¹. The PRAC concluded that as a precautionary measure, Esmya should not be initiated in new patients and in patients who have finalised a previous treatment course, while the review was ongoing. In addition, provisional risk minimisation measures were recommended. Liver function monitoring was recommended, to be performed at least monthly during treatment, up to four weeks after treatment discontinuation, as well as in case a patient shows signs or symptoms compatible with liver injury. In this context, patients who have transaminase levels above 2 times the upper level of normal (ULN) during Esmya treatment should stop treatment and be closely monitored. Furthermore, the PRAC recommended that a healthcare professional communication should be disseminated to inform healthcare professionals about the precautionary measures, awaiting the outcome of the full review of Esmya. The European Commission (EC) issued a decision on the provisional measures on 16 of February 2018. The recommendation on provisional measures was without prejudice to the conclusions for the present procedure under Article 20 of Regulation (EC) No 726/2004.

Available data from non-clinical and clinical studies, as well as spontaneously reported post marketing data, together with relevant information from the literature have now been fully reviewed by the PRAC.

2.2. Safety

The PRAC reviewed all available information regarding liver safety of Esmya, including submissions from the MAH, as well as data provided by National Competent Authorities on the reported cases of liver transplantation. A summary of the relevant information is included below.

¹ More information is available in the published [assessment report on provisional measures](#)

2.2.1. Non clinical safety

The non-clinical safety evaluation of ulipristal acetate included the performance of repeat dose toxicity studies in rodents. Administration of ulipristal acetate (1, 5 and 25 mg/kg/day) to rats in a 6-month toxicity study caused changes in haematological and biochemical parameters. Organ weight analysis showed increased liver and adrenal weights and decreased ovaries, uterus and thyroid weights at the 5 and 25 mg/kg/day dose levels. On histological examination, these correlated with adrenal cortical and liver hepatocyte hypertrophy, ovarian follicular cysts and follicular atresia and uterine glandular dilation.

There were no definitive or apparent correlative data indicating liver toxicity in animals, based on the evaluation of ulipristal acetate in several toxicity studies of different duration, including chronic or life-time testing. The occasional findings of increased liver weight and hepatocellular hypertrophy observed in studies with rodents have been considered as adaptive changes with little relevance to human². In addition, due to hormonal differences between rodents and humans, the toxicological liver safety findings obtained in rodents were assessed as less relevant for humans.

Overall, it is concluded that there are no non-clinical data that indicate that ulipristal acetate would cause drug-induced liver injury (DILI) in humans. Of note, the Food and Drug Administration (FDA) researchers and the Drug-Induced Liver Injury Network (DILIN) have listed chemical sub-groups/types of molecule associated with an increased risk of DILI, and ulipristal acetate does not share structural similarities with these compounds.

The pharmacokinetic profile of ulipristal acetate is well established, including the accumulation profile and the safety margins. Based on the safety profile of ulipristal acetate in the chronic toxicology studies in rat and monkey, the extent of accumulation of ulipristal acetate and its metabolites in the liver is unlikely to be of clinical significance. However, since the primary elimination route of Esmya is via bile/faeces, an increased local exposure in the liver might be possible in existing cholestatic disease states. The major human metabolite of ulipristal acetate is PGL4002 and accounts for 1/4 to 1/2 of ulipristal acetate exposure. Based on in vitro data, ulipristal acetate has the potential to inhibit Cytochrome P450 (CYP) 2D6 and CYP3A4; however, its major metabolite PGL4002 does not inhibit these enzymes. In vitro, the similarity between human, rat, and monkey metabolic pathways was shown. As a general hypothesis for idiosyncratic liver toxicity mechanisms, it could be possible that a reactive metabolite of a drug may covalently bind to a protein and form a hapten-protein adduct, and thereby elicit an adaptive immune response in susceptible individuals. For ulipristal acetate, a minor reactive, partially characterized metabolite has been detected in human faeces, proposed to be a glutathione conjugate of mono-oxygenated ulipristal acetate. This proposed structure is consistent with the oxidation of the 4, 5 carbon atoms to a reactive epoxide, followed by deactivation through glutathione conjugation. There were no signs of formation of this metabolite in vivo in rat or monkey. This metabolite pathway has also been reported for other structurally similar, approved drugs which are not related with idiosyncratic liver toxicity, such as mifepristone.

2.2.2. Clinical safety

2.2.2.1. Clinical studies safety data

The MAH submitted data regarding liver testing and adverse events reported within the hepatic disorders Standardised MedDRA Query (SMQ) throughout the clinical development program.

² Hall AP, Elcombe CR, Foster JR et al. Liver hypertrophy: A review of adaptive (adverse and non-adverse) changes—conclusions from the 3rd International ESTP Expert Workshop. Toxicologic Pathology, October 2012; 40(7):971-94.

In completed clinical trials, over 7,100 subjects have received at least one dose of ulipristal acetate, at all investigated dose levels (1, 2.5, 5, 10, 20, 30, 50, 100, 200 mg oral or 600, 800, 1500, 2500 µg/day or 1 mg/day vaginal ring formulation), in any indication (including emergency contraception, uterine fibroids or healthy volunteers) and for any treatment duration. Multiple doses of ulipristal acetate have been received by 1,975 subjects.

Clinically significant abnormal liver tests were defined as laboratory values meeting Hy's Law criteria³ (alanine aminotransferases (ALT) $\geq 3 \times \text{ULN}$ and simultaneous elevation of bilirubin $> 2 \times \text{ULN}$), or post-screening/baseline elevations of ALT or aspartate aminotransferases (AST) $> 3 \times \text{ULN}$ or total bilirubin $> 2 \times \text{ULN}$.

Phase I

In phase I clinical trials, with up to 10 days multiple daily oral doses, in total 176 subjects were exposed to 2.5, 5, 10, 20 or 50 mg daily. No alterations were observed in liver tests and no liver disorder related AEs were reported for these subjects.

Phase II

In Phase II clinical trials with multiple daily doses, 152 subjects were exposed to 2.5, 5, 10 or 20 mg daily doses. Exclusion criteria in relation to the liver were ALT/AST/ gamma-glutamyltransferase (GGT)/ Alkaline phosphatase (ALP) $> 2 \times \text{ULN}$ (study CDB 2914/2-A), significant abnormalities in laboratory results (studies PGL-N-0287 and PGL-H-0090), hepatic disorder (study PGL-H-510) or alcohol abuse. No liver disorder related Adverse Events (AEs) were reported, and no liver test results of ALT/AST $> 2 \times \text{ULN}$ or total bilirubin $> 1.5 \times \text{ULN}$ were noted in these studies, except study CDB 2914/2-A. In this study, three subjects were reported with liver disorder related AEs, however, the level of ALT/AST was never above 3 times the ULN and bilirubin was never found to be above 2 times ULN at any visit. In one case, a hepatic function disorder was noted at week 8 visit, hepatic steatosis at follow-up 1 month visit and with cholelithiasis 2.5 month after end of treatment; the second case reported abnormal hepatic function at week 8 visit; in the third case, a slightly enhanced enzyme levels was reported at week 4 visit.

Phase III

About 1,500 patients have been included in the phase III program; they were exposed to 5 or 10 mg of ulipristal acetate for up to 8 intermittent 3 month treatment courses.

Four cases of hepatic disorders were reported. The first case was an isolated increase of GGt to $3 \times \text{ULN}$ at a single visit. No other hepatic laboratory values were abnormal during the 13 weeks of treatment and the 6 months of follow up. The second case had cholelithiasis symptoms before inclusion, which worsened during the treatment period. This patient underwent emergency surgery due to obstruction of the small intestine. The third patient had enhanced ALT, AST, and GGT after one month of treatment. The values were reduced at retests 1 and 2 weeks thereafter. Relevant history included ingestion of 500 ml of wine, 48 hours prior to elevated test results, however it is recognised that this is unlikely related to the abnormal level of liver enzymes. The fourth patient had a medical history of hepatic haemangioma and underwent hepatic haemangioma embolization during the study period.

No case meeting the biochemical criteria of Hy's Law was identified in the Phase III program. There were 7 subjects with ALT $> 3 \times \text{ULN}$ and bilirubin $\leq 2 \times \text{ULN}$, 4 subjects with bilirubin $> 2 \times \text{ULN}$ and ALT $\leq 3 \times \text{ULN}$. For these 11 subjects, 9 had alternative explanations and for 2 subjects, the increased values occurred at the follow-up 3 or 6 months visits only.

³ Temple R. Hy's law: predicting serious hepatotoxicity. *Pharmacoepidemiol. Drug Saf.* April 2006; 15(4): 241-3.

2.2.2.2. Post marketing safety data

Cumulative searches of safety databases were performed on post-marketing data of hepatic disorders reported up to 28 February 2018. In addition, follow-up information on 6 serious cases was received up to April 2018. The present review is based on the totality of those data.

Cumulatively, 105 cases within the Standardized MedDRA Query (SMQ) 'Hepatic disorders' have been reported (34 serious and 71 non-serious). In 8 serious cases a possible role of Esmya as a contributing factor was identified, including 4 cases of acute liver failure leading to liver transplantation.

2.2.2.2.1. Cases of acute liver injury leading to liver transplantation

The first case concerns a 55-year old female patient who was diagnosed with acute hepatitis 3 days after completion of the first treatment course with Esmya (treatment duration 109 days); liver transplantation was performed approximately 6 weeks later. Fatigue, asthenia, anorexia and post-prandial fullness occurred 2 days after start of Esmya treatment. These early aspecific symptoms and the histopathological findings of the explanted liver suggest a pre-existing liver disease. Of note, there was no history of alcohol overconsumption or substance abuse and viral hepatitis (Hepatitis A virus (HAV), Hepatitis B virus (HBV), Hepatitis C virus (HCV) and Hepatitis E virus (HEV)) and autoimmune hepatitis was excluded as plausible aetiology. With regards to concomitant medications, cefuroxime 1,500 mg for the treatment of urinary tract infection was taken for 2 days before the diagnosis of hepatitis. A dietary supplement containing lemon balm base, California poppy, hops and passiflora, was taken for 2 days approximately 3 weeks before onset of hepatitis. For this patient, the serology for cytomegalovirus (CMV), Epstein-Barr Virus (EBV) and herpes viruses was not detected; clinical data for the period of acute hepatitis was missing, as well as the reference ranges of liver parameters. The short treatment courses of cefuroxime and dietary supplement are not very plausible as explaining factors for the liver injury. Some data are missing and the lack of reference values makes the interpretation of this case difficult but Esmya remains as a possible (25-50%) contributing factor.

The second case concerns a 58-year old female patient who was diagnosed with acute hepatitis with a time to onset of approximately 2 months. The patient did not use alcohol, had no substance abuse, no intake of herbal medicines or dietary supplements. Normal liver laboratory tests were performed 3 years before the event. After approximately 2 months of treatment with Esmya, the patient suffered from fatigue and nausea, and the treatment was therefore stopped. A week later, fatigue and digestive symptoms became worse and abnormal liver test values were detected. About two weeks after the discontinuation of the treatment, the patient showed jaundice, and hepatic values were still abnormal. Progression from clinically apparent jaundice to encephalopathy occurred within 2 weeks, compatible with acute liver failure. Liver transplantation occurred 4 weeks after stopping Esmya. Viral aetiology was ruled out. Anti-nuclear antibodies (ANA) were positive. The pathological examination of the explanted liver suggested an underlying chronic hepatic condition due to cirrhosis in explanted liver, and with signs of acute necrotising hepatitis. In the parenchyma the hepatocytes show degenerative alterations with cholestasis. The presence of rare plurinucleated regenerative hepatocytes associated with isolated necrosis bodies and Mallory bodies was noted. Although there were no indications of autoimmune disease in the medical history, and the finding of positive ANA is unspecific, an autoimmune cause for the chronic and acute lesions may be possible. A causal role for Esmya in development of acute-on-chronic liver failure is difficult to conclude on, but remains possible. Of note, pre-existing liver cirrhosis might lead to a higher risk for severe DILI⁴. In this case, a role for Esmya as a factor predisposing for an acute on chronic liver failure is possible. Nevertheless, there is remaining

⁴ Chalasani N, Bonkovsky HL, Fontana R et al. Features and outcomes of 899 patients with drug-induced liver Injury: The DILIN Prospective Study. *Gastroenterology*, June 2015; 148(7):1340-52.

uncertainty regarding potential confounding, including whether alcohol may be an alternative explanation, since Mallory bodies were reported.

The third case concerns a 45-year old female patient reported with hepatocellular injury and DILI. Three days after the first dose of Esmya, the patient experienced asthenia, nausea, vomiting and dark urine. At day 26 after the first dose, the patient presented with jaundice and increased hepatic enzymes and Esmya was discontinued due to these events. The patient thereafter worsened, presenting with fulminant hepatitis resulting in liver transplantation about 4 weeks after Esmya discontinuation. The explanted liver was atrophic, weighing 817 g. This could be caused by the massive necrosis in left liver lobe leaving no hepatocytes. Before treatment with Esmya, the patient was reported to be in good health, apart from a previous EBV infection. The patient did not take concomitant medications and no alcohol abuse was reported. Viral hepatitis and autoimmune hepatitis were ruled out, with the exception of Human Herpesvirus 6 (HHV 6), that could not be ruled out. Although no obvious confounding factors are reported, the finding of an atrophic liver may not exclude an acute liver failure as a cause of loss of liver volume but the role of HHV6 is difficult to conclude on. The time to onset (26 days) is relatively short but may be compatible with a DILI causing acute liver failure. The role of Esmya in the development of acute liver failure in this case has been assessed as probable, however uncertainties remain as detailed above.

The fourth case of liver transplantation concerns a 46-year old female patient who was treated with Esmya for approximately 6 months continuously. Even though there are no signs of excessive alcohol intake in the patient history, data on laboratory markers for alcohol induced hepatic damage is lacking. Liver tests were performed and were normal before treatment but no tests were performed during Esmya treatment. Approximately 16 to 20 days after Esmya discontinuation, the patient experienced loss of appetite and nausea, followed by jaundice and rash. At hospitalization, hepatic laboratory values were enhanced, and biopsy showed damage of liver tissue with a pattern indicative of toxic damage. Investigations including hepatitis serology, markers for autoimmune liver disease and Wilsons disease were all negative. A few days later the patient began to develop hepatic encephalopathy, bilirubin 21.1 mg/dl, international normalized ratio (INR) >7 in line with progredient liver failure. The day after, a liver transplantation was performed. A few months later, the patient died, following long-time in intensive care unit due to sepsis, which was out of control due to immunosuppressive therapy. Autoimmune hepatitis and viral hepatitis (i.e. HAV, HBV, HCV, EBV, CMV) were excluded. Approximately 20 days after Esmya discontinuation, hepatitis E IgM were positive and IgG were negative and HEV Ribonucleic acid (RNA) could not be detected in the faeces. In a research letter published in *Lancet*⁵, serial stool and serum samples were collected from 20 patients with acute hepatitis E. Faecal excretion and viremia in these patients were found to be short lived. In 19 patients, all samples obtained after biochemical resolution of hepatitis tested negative; in the remaining patient, HEV RNA was detected in the serum samples but not in stool after biochemical resolution. In line with this, the findings in this fourth case of liver transplantation are difficult to interpret. In addition, there is also some uncertainty regarding the statement about fibrosis in the report, and if that may indicate a longer lasting hepatic disorder. It should also be noted that in cases of DILI with hepatocellular damage, it is more common that ALT is more elevated than AST at least later in the clinical course which was not the case in the description above. Considering the serology data, the finding of hepatitis E, and the relatively long latency time, both being important potential confounding factors, this case is difficult to assess. A role of hepatitis E infection may still be possible although it appears that the finding of HEV IgM was considered unspecific in the clinic where the patient was treated. The temporal relationship for onset of liver injury is not typical. Esmya remains as possible or probable factor for causing liver injury in this case.

⁵ Aggarwal R, Kini D, Sofat S et al. Duration of viraemia and faecal viral excretion in acute hepatitis E. *Lancet*, September 2000; 356(9235): 1081-2.

2.2.2.2.2. Other cases of liver injury

The first case was reported as a DILI, based on increased liver enzymes, which had a time to onset of approximately 3.5-4.5 months. When treatment with Esmya was stopped, weekly liver tests showed steady reduction of high levels of ALT, AST, bilirubin and GGT towards normal. The tests were repeated for 6 weeks. Ibuprofen was reported as a concomitant medication, which may be a confounding factor. There was no strong alternative explanation reported. There is therefore some support for a causal relationship between Esmya and liver injury but uncertainty remains due to missing information.

Another case of a 48 years old woman was reported as necrotising hepatitis occurring at day 10 of the second Esmya treatment course. The patient reported nausea, abdominal pain, extreme fatigue and jaundice, transaminase about 2,500, increased INR and bilirubin. Ulipristal was discontinued. The patient recovered after discontinuation of the treatment. Of note, Sjögren's syndrome was diagnosed at unspecified date. It is acknowledged that Sjögren's syndrome may have liver manifestations, but there is uncertainty about this diagnosis including time relationship with hepatic necrosis and Esmya treatment. Despite possible confounding and missing information, this case reports a positive de-challenge, and a causal role of Esmya is considered possible.

An additional case was reported as cholestatic liver injury occurring on the 10th day of the third treatment course with Esmya. The patient was 39 years old and had a medical history of Hashimoto's thyroiditis. There was limited information on this case. For this case, the causal role for Esmya is difficult to conclude on, taking into account uncertainty regarding potential confounding factors (i.e. concomitant medications) and missing information but remains possible.

A case of 48 years-old women was reported with initial abdominal pain, nausea but normal liver values. An increase of GGT and transferases occurred after 2 months on the second Esmya treatment course. Following ulipristal discontinuation, these returned towards normal. Therefore, a causal relationship with Esmya is possible, but there are remaining uncertainties regarding viral and autoimmune tests. Computed tomography revealed Riedel lobe. The patient's abnormal anatomy and celiac disease may be regarded as confounders although an accessory liver lobe goes mostly without symptoms. Of note, literature data show that Riedels lobe could cause an ischemic liver injury leading to transplantation⁶. However, the role of the accessory liver lobe in this case of serious liver injury is assessed as less plausible, due to the fact that in this patient normal liver values were reported initially, while abnormal liver values would have been expected in association with such abnormal liver lobe.

2.2.2.3. Literature data

The MAH performed a literature review regarding hepatic safety for ulipristal, as well as regarding background occurrence of acute liver failure and DILI. Esmya is not described as a drug often causing liver toxicity in recent publications of DILI^{7,8}). However, these data show limitations, as patients with elevated laboratory parameters were not included in these reviews. Overall, no publication was identified that point to additional concerns in relation to hepatic safety for ulipristal.

2.2.2.4. Discussion on safety

Preclinical and Clinical trial data

⁶ Ladurner R, Brandacher G, Mark W et al. Complete hepatic ischemia due to torsion of a large accessory liver lobe: first case to require transplantation. *Transplant International*. April 2005; 18(4):467-9.

⁷ Björnsson ES. Hepatotoxicity by drugs: The most common implicated agents. *International Journal of Molecular Sciences*. February 2016; 17(2):224.

⁸ Chen M, Suzuki A, Thakkar S et al. DILI rank: the largest reference drug list ranked by the risk for developing drug-induced liver injury in humans. *Drug Discovery Today*. April 2016; 21(4):648-53.

There is no signal of hepatic toxicity from the non-clinical studies, which have been undertaken in rodents and monkey, and which consist of chronic toxicity studies as well as of life time exposure within carcinogenicity studies. However, it is recognised that the non-clinical models used could not be predictive for liver toxicity in humans, due to differences between the species.

The potential toxicity of the major metabolite of Esmya (PGL4002) has not been fully characterised. In vitro studies of ulipristal acetate and PGL4002 are therefore necessary to further investigate its mechanism of action on the liver. In addition, the possibility of perform a physiologically based pharmacokinetic (PBPK) modelling of ulipristal acetate under conditions of impaired bile secretion should also be investigated, in order to assess if an increased local exposure in the liver might be possible in existing cholestatic disease states.

Cumulatively 7,100 subjects have been exposed to at least one dose of Esmya in clinical trials, with 1,077 subjects exposed to ulipristal acetate 5 mg/day or higher for at least one 3-month treatment course. In both the short- and long-term clinical trials median values for liver enzymes (ALT, AST and ALP) and bilirubin remained within the normal range in the Esmya treatment groups. Some reports of elevated hepatic markers were seen, but no more serious events were identified. Of note, both in the phase II and III program, patients with abnormal hepatic laboratory parameters (in most studies ALT/AST/ALP/bilirubin $\geq 2 \times \text{ULN}$), or alcohol abusers, were excluded. Thus, there is no experience from clinical trials of repeated use of ulipristal in patients with pre-existing hepatic disorders. Therefore, the clinical trial data have limited value when assessing the potential risk for hepatic injury.

Post marketing experience

Cumulatively, 105 cases within the SMQ 'Hepatic disorders' have been reported (34 serious and 71 non-serious). In 8 serious cases, some support for a causal role of Esmya as a contributing factor was identified, including 4 cases of acute liver failure leading to liver transplantation. For two of the liver transplantation cases, a contributing role of Esmya was assessed as at least probable, while for the two others, there is insufficient information to either conclude or disregard such relationship as uncertainties due to potential confounding factors remain. There were also 4 other serious cases of liver injury where a role of Esmya is possible although for some of these, data are weak and available information is insufficient to draw firm conclusions. The possible causal associations for these cases are mainly supported by positive de-challenge for some of them, as well as by the absence of other confounding factors, or explanations for the observed liver injury, for others.

In order to have sufficient information to perform a thorough review of cases of liver injury reported with Esmya in the future, the collection of more data on each case is therefore necessary. The use of specific adverse reaction follow up questionnaires is therefore recommended.

Considering the estimated post-marketing exposure to Esmya, the worst case estimation of the number of cases of subacute severe liver impairment leading to liver transplantation appears higher than expected (4 transplantation cases). Moreover, there are 4 other cases with serious liver injury with at least a reasonable possibility for a causal relationship with Esmya. These estimations are not entirely reassuring, although a number of uncertainties were identified.

Time to onset for symptoms of liver injury in the eight cases of liver injury reported range from a few days after the initiation of the treatment to approximately 2 months. In a few cases, symptoms appeared within 2-3 weeks after the discontinuation of the treatment. In some of cases reported in post marketing settings, data are suggestive of an underlying chronic hepatic condition; however, this cannot be concluded for all cases, due to missing information and confounding factors, such as concomitant medications and comorbidities.

The PRAC also noted the experts' view that although a causal relationship cannot be concluded with certainty, based on the safety findings and possible mechanisms, a causal association between Esmya and severe liver injury is plausible. The experts agreed on a possible to probable relationship between Esmya and some cases of severe liver injury. Considering the experts' view, as well as the totality of data considered, including data provided by the MAH, the PRAC was of the view that Esmya may carry a risk for serious liver injury.

The pathogenesis of idiosyncratic DILI is poorly understood. It is likely that DILI arises from several factors including genetic factors, concomitant diseases, age, sex, compound-specific risk factors (e.g. dosage and metabolism characteristics), non-genetic host susceptibility, and environmental factors. Alcohol consumption has also been proposed as a risk factor for DILI from medications, but there is insufficient evidence to support this⁹. With regards to concomitant pathologies, there is no evidence that the history of hepatitis A infection is a risk factor for developing DILI. Acute hepatitis E has been reported to be the cause of some cases of liver disease that were first suspected to be DILI¹⁰. The single carriage of hepatitis B or hepatitis C is not sufficient to be a risk factor of DILI except in patients with chronic hepatitis co-infected with HIV receiving anti-retroviral medication¹¹ or anti-tuberculous treatment¹². Among cases of liver injury reported with Esmya, no firm correlation could be concluded between the incidence of this adverse reaction and a pre-existing hepatitis. However, in order to exclude patients that would be potentially more vulnerable to hepatic insult from the treatment with Esmya, the PRAC considered appropriate to recommend amendments to the product information of Esmya. The indication for intermittent treatment should be restricted, and further amendments to the product information should also be implemented, in order to limit the use of the product to patients which may be more susceptible to liver injury and to monitor liver conditions in patients that are exposed to Esmya.

In view of the remaining uncertainties, the PRAC considers appropriate that further investigations on the impact of Esmya on risk of liver injury are performed. Mechanistic in vitro studies should be carried out, as well as observational studies on patients exposed to Esmya should be performed. In addition, the effectiveness of the risk minimisation measures implemented should also be verified.

2.3. Efficacy

The MAH provided relevant efficacy data including that previously submitted for the initial marketing authorisation on preoperative treatment of uterine fibrosis, as well as the authorisation of the additional indication of intermittent treatment of uterine fibrosis in adult women of reproductive age.

Data on efficacy in pre-operative treatment

The clinical efficacy of ulipristal acetate in the pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age was evaluated in two phase 3 randomised, double-blind, 13 week studies, study PGL07-021 (placebo control) and study PGL07-022 (active control), recruiting patients with very heavy menstrual bleeding associated with uterine fibroids. Key results of these studies are presented in table 1 below.

Table 1: Results of primary and selected secondary efficacy assessments in Phase III studies

⁹ Chalasani N and Björnsson E. Risk factors for idiosyncratic drug-induced liver injury. *Gastroenterology*. June 2010; 138(7): 2246-59.

¹⁰ Davern TJ, Chalasani N, Fontana RJ et al. Acute hepatitis E infection accounts for some cases of suspected drug-induced liver injury. *Gastroenterology*. November 2011; 141(5):1665-72.

¹¹ Andrade RJ, Lopez-Ortega S, Lopez-Vega MC et al. Idiosyncratic drug hepatotoxicity: a 2008 update. *Expert Rev. Clin. Pharmacol.* March 2008; 1(2):261-76.

¹² Kim WS, Lee SS, Lee CM et al. Hepatitis C and not Hepatitis B virus is a risk factor for anti-tuberculosis drug induced liver injury. *BMC Infectious Diseases*. February 2016; 16-50.

Parameter	PGL07-021			PGL07-022		
	Placebo N=48	Ulipristal acetate 5 mg/day N=95	Ulipristal acetate 10 mg/day N=94	Leuprorelin 3.75 mg/ month N=93	Ulipristal acetate 5 mg/day N=93	Ulipristal acetate 10 mg/day N=95
Menstrual bleeding						
Median PBAC at baseline	376	386	330	297	286	271
Median change at week 13	-59	-329	-326	-274	-268	-268
Patients in amenorrhea at week 13	3 (6.3%)	69 (73.4%)¹	76 (81.7%)²	74 (80.4%)	70 (75.3%)	85 (89.5%)
Patients whose menstrual bleeding became normal (PBAC < 75) at week 13	9 (18.8%)	86 (91.5%)¹	86 (92.5%)¹	82 (89.1%)	84 (90.3%)	93 (97.9%)
Median change in myoma volume from baseline to week 13 ^a	+3.0%	-21.2%³	-12.3%⁴	-53.5%	-35.6%	-42.1%

^a In Study 1, change from baseline in total myoma volume was measured by magnetic resonance imaging (MRI). In Study 2, change in the volume of the three largest myomas was measured by ultrasound. Bold values in shaded squares indicate that there was a significant difference in the comparisons between ulipristal acetate and the control. These were always in favour of ulipristal acetate. P values: ¹ = <0.001, ² = 0.037, ³ = <0.002, ⁴ = <0.006.

In study PGL07-021, a statistically significant difference was observed in reduction in menstrual blood loss in favour of the patients treated with ulipristal acetate compared to placebo, resulting in faster and more efficient correction of anaemia than iron supplement alone. Likewise, patients treated with ulipristal acetate had a greater reduction in myoma size, as assessed by MRI. In study PGL07-022, the reduction in menstrual blood loss was comparable for the patients treated with ulipristal acetate and the active comparator, leuprorelin 3.75 mg, a gonadotrophin releasing hormone-agonist. Most patients treated with ulipristal acetate stopped bleeding within the first week of treatment (amenorrhea). In addition, an evaluation of quality of life improvement in treatment groups was performed through measurement of discomfort due to symptoms of uterine fibroids; a significant improvement in the ulipristal acetate groups versus placebo was demonstrated.

Data on efficacy in intermittent treatment

The therapeutic indication for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age was based on results from study PGL11-006 providing data for up to 4 intermittent treatment courses of 3 months each with ulipristal acetate along with data for repeated treatment courses from the previous studies, including the open-label study PGL09-027. Study PGL11-006 evaluated the efficacy and safety of ulipristal acetate 5 mg and 10 mg daily dose. The inclusion and exclusion criteria of study PGL11-006 were largely in line with those used in previous studies for short term treatment, except that the women included in study PGL11-006 were not required to be eligible for a surgical procedure for their uterine fibroids.

A summary of results of primary and selected secondary efficacy assessment in long term phase III studies is presented in table 2 below:

Table 2: Results of primary and selected secondary efficacy assessments in long term Phase III studies

Parameter	After treatment course 2 (two times 3 months of treatment)			After treatment course 4 (four times 3 months of treatment)		
	PGL09-027 ^a	PGL11-006		PGL09-027	PGL11-006	
Patients starting treatment course 2 or 4	10 mg/day N=132	5 mg/day N=213	10 mg/day N=207	10 mg/day N=107	5 mg/day N=178	10 mg/day N=176
Patients in amenorrhoea ^{b,c}	N=131	N=205	N=197	N=107	N=227	N=220
	116 (88.5%)	152 (74.1%)	162 (82.2%)	96 (89.7%)	158 (69.6%)	164 (74.5%)
Patients with controlled bleeding ^{b,c, d}	NA	N=199	N=191	NA	N=202	N=192
		175 (87.9%)	168 (88.0%)		148 (73.3%)	144 (75.0%)
Median change in myoma volume from baseline	-63.2%	-54.1%	-58.0%	-72.1%	-71.8%	-72.7%

^a Treatment course 2 assessment corresponds to Treatment course 2 plus one menstrual bleeding.

^b Patients with missing values were excluded from the analysis.

^c N and % include withdrawn patients

^d Controlled bleeding was defined as no episodes of heavy bleeding and a maximum of 8 days of bleeding (not including days of spotting) during the last 2 months of a treatment course.

Final results of study PGL11-006 showed that 73.3 % of the patients on the 5 mg dose had controlled bleeding (no episodes of heavy bleeding and a maximum of 8 days of bleeding over 56 days) after treatment course 4 which is considered to be of clinical relevance. In addition, the proportions of patients in amenorrhoea after each treatment course are of clear clinical relevance supporting repeated intermittent treatment with ulipristal acetate.

Of note, during the off-treatment interval, with resumption of menstruation the quality of life was slightly reduced compared to the end of each treatment course, but was still improved in comparison to baseline.

Discussion on efficacy

The two short-term studies demonstrated the ability of the active substance to reduce fibroid-related bleeding, anaemia and fibroid size if administered in a daily dose of 5 mg for up to three months, in women who were to undergo surgery for their fibroids.

Esmya was also shown to be effective at reducing bleeding and uterine fibroid size when used intermittently for longer periods (up to 4 treatment courses) and improved quality of life. Data for up to 8 treatment courses are available from a limited number of women.

3. Experts consultation

The PRAC consulted an ad-hoc experts group, which provided advice on a number of issues.

There was a consensus among physicians and patients that the symptomatic benefits associated with Esmya are important for at least some patients, based on the current knowledge of benefits. However, this does not mean that Esmya should be the preferred treatment for all patients. The experts' views varied on the importance of the benefits associated with Esmya. According to some experts, the

benefits were marginal. Although the effects on bleeding are not disputed, the reduction in size of fibroid has been less convincing (+/-10%) in the study where observers were blinded to treatment allocation. There is likely misinformation about the claim that surgery can be avoided altogether. Definitive avoidance of surgery has not been established, and the benefits of delaying surgery are also not proven since delaying surgery might theoretically result in less effective or more invasive surgery due to larger fibroids. Similarly, long-term effects, effects on fertility, and Quality of Life data about the benefits of Esmya compared to other medical therapy, minimally invasive procedures (e.g. uterine artery embolisation), and surgery, are not known. Other experts focussed on the importance of having different medical treatment options, especially for long-term treatment, and the advantages compared to gonadotropin-releasing hormone (GnRH) agonists which are associated with adverse effects, such as hypo-oestrogenism and decreased bone mineral density, in the pre-operative setting.

Unfortunately, long-term data comparing different modalities (including hysterectomy) are lacking. Based on the available evidence it is difficult to suggest a specific population that might benefit the most from Esmya, as much will depend on individual preferences. Although not based on robust data, it is likely that invasive options will be preferred for managing the disease in the long-term and avoiding risks associated with Esmya, while other patients may want to avoid more radical surgical options and preserve fertility. Size, number and location of fibroids may also inform the decision. In the short-term pre-operative setting (preoperative treatment for 3 months), GnRH agonists may be the preferred option to avoid the risks of severe liver injury associated with Esmya. Adequate information to physicians and patients on benefits, risks and uncertainties of available options are paramount for adequate medical decisions. There were concerns that currently the product might be prescribed off-label. For instance, the indication is restricted to women of reproductive age while many of the cases described with hepatic toxicity were older than 55. Although statistically possible, this may indicate off-label use in postmenopausal women. It should be stressed that the benefits and risks in post-menopausal women have not been established.

From the available evidence and knowledge about pathophysiology of fibroids and mechanism of action of ulipristal acetate, a causal relationship cannot be concluded with certainty. However, based on the safety findings and possible mechanisms, there was consensus that a causal association between Esmya and severe liver injury is plausible. Concerning potential mechanisms, it is possible to speculate that exacerbation of autoimmunity or an indirect estrogenic effect due to modulation of progesterone activity could play a role. Concerning the clinical safety findings, in many cases the causality assessment by the company was negative (based for instance on confounding factors, lack of the exclusion of competing aetiologies; viral infection), but this was debateable (there was broad consensus among hepatologists that at least 2/7 cases were most likely related to the use of ulipristal). The experts agreed on a possible to probable relationship between Esmya and some cases of severe liver injury. As known, a potential mechanism for the occurrence of DILI is difficult to elucidate. Concerning other aspects, these could not be discussed in depth since they remain highly speculative and not evidence-based. No strong conclusions could be drawn about additional factors associated with DILI based on available data.

Some experts argued that monthly liver function tests will not be effective or that compliance would be poor. Others emphasized that they would draw the attention of physicians on the risk of liver toxicity. Others still questioned if treatment initiation shouldn't be restricted to gynaecologists. Nevertheless, the experts agreed that ALT testing at the start of treatment is a reasonable step, although there is no evidence that this will prevent ulipristal DILI. Follow up with regular ALT measurements will likely be inefficient but is the only safety net that can be recommended to detect cases (astute clinical vigilance would be a better solution but that requires awareness of the issue from the attending physician, which may not always be the case). Overall, the proposed measures (contraindication; warnings), although not based on data from cases with associated hepatotoxicity, appear reasonable and proportionate

without the need of major additions or modifications (minor modification: bilirubin alone should not be a criterion for not initiating treatment). The emphasis on when to stop treatment was agreed.

General symptoms (fatigue) shortly after start of treatment could also be an early signal (alert).

In conclusion, the proposed measures were considered appropriate. However, there is no evidence that the measures proposed will be effective in avoiding further liver injuries, including severe events. This is due to the fact that the risk factors for liver injury have not been identified.

A number of studies would be useful. A first objective is to confirm what appears to be a plausible causal relationship between Esmya and severe liver injury, and this could be done on the basis of non-clinical as well as clinical studies (e.g. registry study with treated patients). Concerning non-clinical studies a number of approaches are possible and a comprehensive strategy should be proposed by the company. Concerning clinical studies, an observational safety study (registry) looking at liver tests before, during and after treatment, possible risk-factors and confounders, could be useful in the real-life setting (also to clarify the patients and disease characteristics of patients). Together with mechanistic studies, investigating autoimmune and hormonal mechanisms, this should allow a better understanding of the risk and associated factors, and refining risk-minimisation measures, as appropriate.

4. Benefit-risk balance

Esmya (ulipristal acetate, 5 mg) is a centrally authorised medicinal 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.

PRAC considered all the data submitted by the MAH, as well as data provided by the National Competent Authorities including follow-up information on cases of liver transplantation. The views expressed by *ad-hoc* experts consulted during the course of the procedure were also considered.

Uterine fibroids are the most common female pelvic tumour. Although uterine fibroids are benign, moderate to severe forms are often associated with significant morbidity, such as heavy bleeding, anaemia, pain, discomfort and reduced quality of life. As assessed in the initial marketing authorisation of Esmya, the clinical efficacy of ulipristal acetate in the pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age was based on short-term studies demonstrating the ability of the active substance to reduce fibroid-related bleeding, anaemia and fibroid size if administered in a daily dose of 5 mg for up to three months. The marketing authorisation of Esmya was extended to include the therapeutic indication for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. This last indication was authorised based on results from another study providing data for up to 4 intermittent treatment courses of 3 months each with ulipristal acetate along with data for repeated treatment courses from the previous studies. Through a pronounced reduction of bleeding, reducing anaemia and related symptoms, Esmya has been demonstrated to rapidly contribute to the improvement of the quality of life in patients who did not undertake a surgical treatment. Of note, menopause constitutes a natural end to the need for treatment.

It was noted that no signal of hepatic toxicity was identified from non-clinical or clinical studies on Esmya. However, due to exclusion criteria covering patients with elevated transaminases, or other signs of liver disease, as well as the limited size of the safety database in these studies, the absence of findings in clinical trials has to be interpreted with caution. Also, due to hormonal differences between rodents and humans, the toxicological liver safety findings obtained in rodents were assessed as less relevant for humans. In post marketing settings, all of the reported cases lack information hampering

causality assessment, and causal relationship with Esmya and serious hepatic injury is therefore not firmly established. However, there is sufficient information from these cases to conclude that there is at least a reasonable possibility that Esmya may infrequently contribute to hepatic injury.

Based on the safety findings and possible mechanism of action, the experts of the ad hoc experts group were of the view that a causal association between Esmya and severe liver injury is plausible. In particular, there was a consensus among hepatologists that in at least 2 cases reported, a relation with the use of Esmya could be observed.

Although the general characteristics of Esmya do not support it to be a typical DILI causing agent, based on the current review, and taking experts views into consideration, the PRAC concluded that Esmya (ulipristal acetate) may carry a risk for serious liver injury. The available data raise serious concerns, and warrant risk minimisation measures to be taken.

Uterine fibroids are the single most common indication for hysterectomy¹³. Hysterectomy is a very common curative surgical procedure within gynaecology associated with a low mortality (mortality figures quoted range from 0.02% to 0.17%) and a low risk of intra- or postoperative complications (quoted from 5% to 8%). Other surgical treatments such as myomectomy and uterine artery embolisation are also valid alternatives to hysterectomy, but they are not suitable for all cases and are also associated with a higher rate for complications than hysterectomy. However, it is recognised that a surgical treatment is not suitable for all women, due to their medical history, co-morbidities or willingness to preserve fertility.

In view of the existing concerns on recently reported cases of serious liver injury and acknowledging that the magnitude of the benefit differs for different clinical situations, the PRAC considered that the use of Esmya should be limited. Taking into account the clinical utility of Esmya in the intermittent treatment indication, where no other long-term pharmacological alternative is authorised, this indication should be limited to adult women of reproductive age who are not eligible for surgery.

The pre-operative treatment may be considered of least benefit as it reflects a situation when surgery is planned; however reductions in myoma size as well as reductions in blood loss and anaemia are considered of clinical significance. PRAC considered that it should be clarified in the wording of the indication that in line with the current posology Esmya is to be used for a single treatment course in pre-operative setting.

Taking into account the experts' views on the topic, and after a thorough review of the available data, PRAC considered that the following risk minimisation measures should be recommended.

In order to exclude patients that would be potentially more susceptible to hepatic insult from the treatment with Esmya, the product should be contraindicated in patients with underlying hepatic disorder. In addition, the PRAC considers that warnings regarding monitoring and stopping criteria should be implemented, in order to identify a hepatic injury of any origin before the patient experiences symptoms, which could reduce the risk of developing serious injury.

Therefore, liver function tests should be performed before starting treatment with Esmya, monthly during the first two courses of treatment as well as two to four weeks after the discontinuation of the treatment. In line with the exclusion criteria in the clinical studies of Esmya, patients with ALT or AST > 2 x ULN (isolated or in combination with bilirubin >2 x ULN) should not initiate treatment. In addition, patients who develop transaminase levels (ALT or AST) > 3 x ULN during treatment should stop treatment and be closely monitored. Usually, DILI events occur within the first 6 months after starting

¹³ Stewards EA; Uterine Fibroids. Lancet, 27 January 2001; 357(9252):293-8.

a new medication¹⁴. Based on the reported post-marketing cases of potential liver injury with Esmya, and assuming that all such cases are due to Esmya, regardless of causality, the peak time to onset of liver injury is around 140 days and the vast majority of the reported potential drug induced liver injuries occurring between 1 and 8 months (2 treatment cycles including 2 months pause). This is the rationale that justifies the mandatory liver monitoring within the first 2 treatment courses, while during later courses, monitoring is recommended as clinically indicated. Of note, the development of drug induced liver injury generally tends to be a gradual phenomenon, developing over 1-4 weeks. More frequent monitoring than monthly is not considered practically feasible. The PRAC considers it appropriate to also monitor liver function 2 to 4 weeks after the treatment has stopped, since for some of the reported cases, liver injury was reported a few weeks after the discontinuation of the treatment.

In order to ensure that decisions on the initiation and continuation of the treatment are made by physicians who are familiar with diagnosis of uterine fibrosis, the PRAC also recommends that the initiation and supervision of treatment with Esmya should be restricted to physicians experienced in the diagnosis and treatment of uterine fibroids.

The existing educational material (physician's guide) should also be updated with these recommendations, and the issuing of a Direct Healthcare Professional Communication (DHPC) is also considered appropriate, to inform healthcare professionals of the recommendations of the present review. In order to ensure that patients are adequately informed on the possible risks of liver injury and the implemented risk minimisation measures, a patient card should be issued. Patients should be informed of potential adverse reactions related to liver that could be caused by the use of Esmya, as well as on the need to warn their physicians on any liver problems they may have. Patients should inform physicians on any liver problems they may have, and be also aware of the liver function monitoring tests to be performed before the treatment, during the treatment and after its discontinuation.

The PRAC was also of the view that the reported cases of liver injury should be closely monitored; to this effect a targeted follow up questionnaire has been included in a revised risk management plan (RMP). The MAH should implement these questionnaires and their results should be discussed in future periodic safety update reports (PSURs).

In the view of the remaining uncertainties, the PRAC is of the view that further data on Esmya and liver injury should be collected. The PRAC considers that in vitro studies should be performed by the MAH, in order to better characterize the mechanistic profile of DILI as associated with Esmya. In addition, in order to analyse data on risk of liver injury related with Esmya and on effectiveness of risk minimisation measures, observational studies should be performed.

In conclusion, the PRAC considered that the benefit-risk balance of Esmya remained favourable subject to the amendments of the terms of the marketing authorisations. The temporary measure recommended by the PRAC in February 2018, to not treat any new patients is superseded by these new recommendations.

5. Risk management

The MAH should operate a risk management system described in a RMP which has been endorsed as part of the current review procedure. The PRAC considered that DILI should be classified as an important identified risk in the RMP of Esmya.

¹⁴ Chalasani NP, Hayashi PH, Bonkovsky HL et al. ACG Clinical Guideline: The diagnosis and management of idiosyncratic drug-induced liver injury. *The American Journal of Gastroenterology*. July 2014; 109(7):950-66.

The following ongoing and planned activities are considered relevant to better characterise this risk and should be reflected in the RMP.

5.1. Pharmacovigilance activities

5.1.1. Specific adverse reaction follow-up questionnaires

The PRAC considered that targeted follow-up questionnaires are necessary in order to collect more data and allow in depth review of cases of liver injury. The targeted questionnaire should include the following sections: medical history, symptoms of liver injury, laboratory testing, imaging (ultrasound, Computer Tomography, MRI), histopathology, and causality assessment. Only questions relevant for a particular case, depending on the already available information, should be sent to the reporter. Analyses of the data collected via the existing targeted follow-up forms for serious hepatic injury should be presented in future PSURs.

5.1.2. Non-clinical studies

The MAH should perform in vitro mechanistic studies, to further explore possible mechanisms for DILI, as detailed below.

Ulipristal acetate and its main metabolite (PGL4002) should be tested in vitro for their potential to inhibit multidrug resistance-associated protein 2 (MRP2) in membrane vesicles. In addition, an evaluation of the effect of ulipristal acetate on cell viability in vitro should be performed. This evaluation should be conducted in 3D spheroid micro tissues made from primary human hepatocytes co cultured with non-parenchymal cells for up to 14 days. Additional transcriptomics experiments will be performed to gain insight into the possible mechanisms. The effect of ulipristal acetate and PGL4002 on cell viability in sandwich cultured primary human hepatocytes should be also evaluated. The potential for ulipristal acetate and its metabolites to cause cholestatic effects will be assessed by comparing the cell viability between incubations with and without added bile salts.

The MAH should also perform a feasibility assessment of PBPK modelling of ulipristal acetate under conditions of impaired bile secretion. If feasible, the study should be conducted and the concentrations of ulipristal acetate and PGL4002 in human blood and liver will be estimated in a PBPK model in which bile secretion is impaired.

All the above described mechanistic studies should be included as category 3 of the RMP. The studies should start in June 2018 and the study report should be submitted by September 2018.

5.1.3. Non-interventional studies

Observational studies on hepatic risk

In order to define the impact of Esmya on hepatic risk, PRAC considers that several observational studies should be performed, some of which subject to feasibility assessment. These studies should be categorised as category 3 studies in the RMP.

A retrospective cohort study should be performed, based on multinational database. The study objective should be to estimate the absolute and relative risk of liver injury with Esmya treatment and compare with patients with uterine fibroids not taking Esmya. The feasibility assessment of various EU national databases is ongoing. One of the databases is the Clinical Practice Research Datalink (CPRD), covering over 6 million active patients in the UK. Based on the feasibility assessment result, the study will be conducted or cancelled due to lack of statistical power. The MAH is required to submit the

protocol of this category 3 study to the EMA for assessment by the PRAC, within 3 months of adoption of the European Commission decision.

The MAH has also proposed a retrospective case control study utilizing medical records of transplantation centres in at least five EU member states. This study could be performed to estimate the overall population based absolute risk of acute liver failure leading to registration for transplantation in women exposed to Esmya. However, it is noted that the study would not provide additional information regarding the association between Esmya and DILI not leading to transplantation. The performance of this study is subject to feasibility; the feasibility report should be submitted to the PRAC within two months from the EC Decision of the present procedure.

A feasibility assessment of an observational study using EU registries with biomarker data should be performed. Examples of these registries are THIN (United Kingdom), GePaRD (Germany), Pro-EURO DILI registry, Spanish registry and iDILIC registry. The intent of the study is to describe trends in biomarkers for hepatic injury following exposure to Esmya and the proportion of patients developing clinically relevant increases in biomarkers for hepatic injury. It should also describe adherence to monitoring of biomarkers for hepatic injury, and identify risk factors for DILI. The feasibility report should be submitted to the PRAC within two months from the EC Decision of the present procedure.

In addition to the above, a genetic analysis (HLA) study should be performed, through a retrospective and prospective analysis of blood samples provided voluntarily by the patients. Data used could be from EU registries with biomarker data in patients with severe DILI in registries such as, the International DILI Consortium (iDILIC), Spanish registry and the Pro-EURO DILI registry. Feasibility study will be performed prior to initiation of this study, for which the feasibility report should be submitted to the PRAC within two months from the EC Decision of the present procedure.

Observational studies on effectiveness of risk minimization

A retrospective drug utilisation study should be performed, through a chart review across not less of four major EU countries. The study should measure effectiveness of monitoring of liver parameters in patients treated with Esmya, adherence to the modified indication and to the contraindication of underlying hepatic disorder. Protocol submission for this study to the PRAC should be within three months from EC decision on the present procedure.

In order to measure effectiveness of the recommended risk minimisation measures in patients treated with Esmya, EU registries should be used, e.g. THIN, GePaRD, Pro-EURO DILI registry and the DILI registry databases. This study is subject to feasibility; feasibility report should be submitted to the PRAC within two months after EC decision of the present procedure.

5.2. Risk minimisation measures

5.2.1. Amendments to the product information

The PRAC considered that routine risk minimisation measures in the form of updates to the product information would be necessary in order to minimise the risk of hepatic injury associated with the use of Esmya. These changes include amendments to sections 4.1, 4.2, 4.3, 4.4, 4.8 and 5.2 of the SmPC.

The intermittent treatment of moderate to severe symptoms of uterine fibroids with Esmya should be restricted to adult women of reproductive age who are not eligible for surgery. It is also clarified that Esmya should be used as one treatment course only of pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. The PRAC also recommended that the initiation and supervision of treatment with Esmya should be restricted to physicians experienced in the diagnosis and treatment of uterine fibroids.

The PRAC further concluded that Esmya should be contraindicated in patients with underlying hepatic disorder. As a warning, PRAC recommends that liver function tests must be performed before starting the treatment with Esmya, during treatment as well after its discontinuation. The levels of hepatic enzymes above which the product should not be used or should be discontinued are specified in the SmPC. In addition, patients who show signs or symptoms compatible with liver injury during treatment should discontinue it and be investigated immediately.

Furthermore, hepatic failure has been added in the list of adverse reactions, with a frequency not known.

The Package Leaflet was amended accordingly.

The Annex II of the marketing authorisation was also updated to reflect the key elements to be included in the existing educational materials and in the newly introduced patient card in relation to the risk of liver injury.

5.2.2. Direct Healthcare Professional Communication/Communication plan

A Direct Healthcare Professional Communication (DHPC) was disseminated in February 2018 based on the preliminary data available to inform HCPs of the provisional measures to restrict the use of Esmya to patients currently under treatment, and to introduce liver monitoring.

The PRAC considered that another DHPC should be disseminated to inform healthcare professionals of the conclusions of the present review. The wording of a DHPC was adopted to communicate the agreed amendments to the product information, including the restriction of the indication to patients who are not eligible for surgery, the introduction of the contraindication for patients with underlying liver disorders and the necessity of liver tests to be performed before, during and after the treatment. The relevant hepatic enzyme levels are specified, for which the treatment should not be initiated or should be discontinued if detected during treatment. The DHPC should also specify the need for healthcare professionals to inform patients of signs and symptoms of liver injury, and to stop the treatment should these symptoms appear.

The PRAC also agreed on a communication plan.

5.2.3. Educational materials

The Physician's guide to prescribing that is in Annex II of the Marketing Authorisation of Esmya should be amended with the addition of the following key elements:

- Patients with underlying hepatic disorder are contraindicated.
- Baseline liver function tests are required before treatment initiation, and before each new treatment course.
- Patients with alanine transaminase (ALT) or aspartate aminotransferase (AST) > 2 x ULN (isolated or in combination with bilirubin >2 x ULN) must not be treated.
- Liver function must be monitored monthly during the first 2 treatment courses, and thereafter when clinically indicated.
- Treatment must be stopped if the patient develops ALT or AST > 3 x ULN.
- If a patient during treatment shows signs or symptoms compatible with liver injury, treatment should be stopped, and the patient should be investigated immediately, and liver function tests performed.

- In addition, liver testing should be performed within 2-4 weeks after treatment has stopped.

In addition to the above, an educational material for patients in the form of a patient card should be added to Annex II of the Marketing Authorisation of the product, and is fully described in Annex III of the marketing authorisation. Key elements are the following:

- Inform the patients about potential adverse reactions related to liver that could be caused by the use of Esmya.
- Inform the patients on the need to warn their physicians on any liver problems they may have.
- Inform the patients not to take Esmya in case of liver problems.
- Inform the patients about the need for monitoring of liver function before starting each treatment course, monthly during treatment and within a few weeks after the treatment has stopped.

The patient card should be included in the secondary packaging of the medicinal product. With regards to medicinal products that are already on the market, patient cards will be provided to pharmacists to be inserted in the packages containing Esmya.

6. Grounds for Recommendation

Whereas,

- The PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data for Esmya (ulipristal acetate).
- The PRAC reviewed the totality of the data regarding the risk for liver injury with Esmya provided by the marketing authorisation holder and National Competent Authorities on cases of liver injury and liver transplantation reported since the initial marketing authorisation of the product. Data from clinical trials, non-clinical studies including in vitro testing were also reviewed. The PRAC also considered the views expressed by experts at an ad hoc expert group meeting.
- The PRAC concluded that Esmya (ulipristal acetate) may carry a risk for serious liver injury. While uncertainties around causality remain, PRAC recognised the very serious outcome of the reported cases of liver injury. Balancing this to the benefits of Esmya treatment of moderate to severe symptoms of uterine fibroids, the PRAC concluded that the indicated population should be restricted for safety reasons. Furthermore, measures to minimise a risk for liver injury should be implemented.
- The PRAC recommended that intermittent treatment of moderate to severe symptoms of uterine fibroids with Esmya should be restricted to adult women of reproductive age who are not eligible for surgery. It is also clarified that Esmya can be used as one treatment course of pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. The PRAC also recommended that the initiation and supervision of treatment with Esmya should be restricted to physicians experienced in the diagnosis and treatment of uterine fibroids.
- The PRAC further concluded that Esmya should be contraindicated in patients with underlying hepatic disorder. In addition, the PRAC recommended the performance of liver function tests before starting each treatment course with Esmya, during treatment as well as two to four weeks after the discontinuation of treatment. Guidance on treatment initiation and

discontinuation based on the results of these tests is included in the product information. Treatment should be stopped in patients showing signs or symptoms compatible with liver injury and the patient should be investigated immediately.

- The PRAC also found it necessary to introduce a patient card to be provided in each package of Esmya, to ensure that patients are adequately informed on the possible risks of liver injury and the implemented risk minimisation measures. In addition, the existing physician's guide to prescribing should be updated accordingly.
- The PRAC was also of the opinion that mechanistic studies should be conducted, to further investigate a possible mechanism for hepatic toxicity. In addition, observational studies should be performed to further characterise the hepatic risk and to evaluate the effectiveness of implemented risk minimisation measures.

In view of the above, the Committee considers that the benefit-risk balance of Esmya (ulipristal acetate) remains favourable subject to the agreed amendments to the product information and the additional risk minimisation measures. The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for Esmya (ulipristal acetate).

Appendix 1

Divergent positions

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

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

Esmya (INN: ulipristal acetate)

Divergent statement:

The following PRAC Members consider that even if the agreed PI changes and RMP update are implemented, the benefit risk ratio of Esmya is not favourable based on the following grounds:

Rare but very severe hepatic failures occurred in patients treated with Esmya. A causal relationship is far from excluded and is even likely in some cases. There are no elements to define a toxic mechanism or risk factors that could have predicted these events and that could be a basis for an efficient prevention strategy.

Esmya demonstrated a benefit in controlling symptoms (bleeding) in uterine fibroma. There is no convincing evidence that treatment with Esmya will avoid surgery or show a favourable Benefit/Risk balance in the long term. Regarding short term treatment (<3 months) in a pre-operative context, according to the experts from ad hoc expert group conclusions, available medical alternatives (such as GnRH agonists) demonstrated similar benefits without any relevant risk of hepatic failure and would be a preferable option for short term treatment for a pre-operative purpose.

The benefits established with Esmya in the broad modified indications accepted by the PRAC majority are limited as efficacy and safety have not been established with certainty in the proposed population. In pre-operative treatment, alternatives exist and Esmya is no longer considered as a suitable medicinal option. For intermittent treatment of fibroids, only a last line indication, to control severe symptoms of the disease when surgery is impossible and when other medical treatments are not an option, would have been acceptable in light of the severe risks observed.

The amendments adopted by the PRAC majority to the product information and RMP will unfortunately not prevent the hepatic risk and not limit these concerns.

Therefore, we consider that in the PRAC's proposed indications for Esmya, the risk (especially hepatic) continue to outweigh benefit leading to a negative B/R balance.

PRAC Members expressing a divergent opinion:

- Ghania Chamouni
- Stephen J.W. Evans
- Thierry Trenque

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

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

Esmya (INN: ulipristal acetate)

Divergent statement:

The following PRAC Members consider that even if the agreed PI changes and RMP update are implemented, the benefit risk ratio of Esmya is not favourable based on the following grounds:

Rare but very severe hepatic failures occurred in patients treated with Esmya. A causal relationship is far from excluded and is even likely in some cases. There are no elements to define a toxic mechanism or risk factors that could have predicted these events and that could be a basis for an efficient prevention strategy.

Esmya demonstrated a benefit in controlling symptoms (bleeding) in uterine fibroma. There is no convincing evidence that treatment with Esmya will avoid surgery or show a favourable Benefit/Risk balance in the long term. Regarding short term treatment (<3 months) in a pre-operative context, according to the experts from ad hoc expert group conclusions, available medical alternatives (such as GnRH agonists) demonstrated similar benefits without any relevant risk of hepatic failure and would be a preferable option for short term treatment for a pre-operative purpose.

The benefits established with Esmya in the broad modified indications accepted by the PRAC majority are limited as efficacy and safety have not been established with certainty in the proposed population. In pre-operative treatment, alternatives exist and Esmya is no longer considered as a suitable medicinal option. For intermittent treatment of fibroids, only a last line indication, to control severe symptoms of the disease when surgery is impossible and when other medical treatments are not an option, would have been acceptable in light of the severe risks observed.

The amendments adopted by the PRAC majority to the product information and RMP will unfortunately not prevent the hepatic risk and not limit these concerns.

Therefore, we consider that in the PRAC's proposed indications for Esmya, the risk (especially hepatic) continue to outweigh benefit leading to a negative B/R balance.

PRAC Member expressing a divergent opinion:

- David Olsen