



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee (PRAC)

## Assessment report on provisional measures

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 with all information of a commercially confidential nature deleted.



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# 1. Information on the procedure

Four cases of serious liver injury leading to a hepatic transplantation were reported since the marketing authorisation of Esmya. In addition, several other cases of hepatic impairment associated with the use of the product were reported. Given the estimated exposure to Esmya of approximately 175,000 patient years, the number of cases of subacute severe liver impairment leading to liver transplantation with Esmya appears higher than expected, although background incidence on drug induced liver injury is uncertain. No information on hepatic events is currently 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. Three out of those four cases of serious liver injury were reported to the competent authorities before November 2017. The possible causal relationship between Esmya and acute liver failure of those three cases prompted an in-depth investigation of this risk and its impact on the benefit risk balance of Esmya is warranted.

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.

A fourth case of hepatic liver failure leading to transplantation was reported on 30<sup>th</sup> of January 2018. Taking into account this new case and the totality of the reported cases, a preliminary review and assessment of all data available was performed by PRAC, to consider if provisional measures were needed while the issue is being furtherly reviewed. The preliminary review was concluded on 8<sup>th</sup> of February 2018. The current report relates only to provisional measures recommended by the PRAC for Esmya based on the preliminary data available at this time. These provisional measures are without prejudice to the outcome of the ongoing review under Article 20 procedure.

## 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.

Esmya has been firstly authorised in the European Union on 23 February 2012. The post-marketing exposure to Esmya is estimated to be at around 700,000 patients so far. Although the duration of exposure is uncertain for the post-marketing experience, a mean duration of 3 months is considered a reasonable assumption. This results in that the reported patient exposure is estimated to correspond to 175,000 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 (approximately 30,000 patients), Germany (approximately 32,000 patients), Italy (approximately 24,000 patients) and Spain (approximately 30,000 patients).

Currently 12 studies are ongoing with Esmya 5 mg tablets. One study (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, some non-interventional, and some interventional; with up to 100 patients/study. Most of these studies are in patients with 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. There is also one phase I study.

Cumulatively, 51 cases of hepatic impairment associated with the use of Esmya were reported, of which 17 were serious and 34 were non serious, corresponding 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 could be plausible, and considering the seriousness of the reported cases, a review under Article 20 of Regulation (EC) No 726/2004 was initiated to review the risk of liver injury and its impact on the benefit-risk balance of the medicinal product. An additional case of acute liver injury was reported after the initiation of this review. This is a spontaneously reported case for which limited follow up data could be collected and reviewed. In this recently reported case, serious hepatic failure lead to transplantation, followed by a fatal outcome a few months later, due to sepsis experienced after the liver transplant.

## **2.2. Clinical aspects**

### **2.2.1. Efficacy**

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. In patients suffering from heavy menstrual bleeding associated with uterine fibroids, repeated 3-month treatment courses with ulipristal acetate provide a medical alternative to surgery and have the potential to reduce the need for surgical intervention.

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. Study PGL11-006 evaluated the efficacy and safety of ulipristal acetate 5 mg and 10 mg. The inclusion and exclusion criteria of study PGL11-006 were largely in line with those used in previous studies, with the exception that the women included in this study were not required to be eligible for a surgical procedure for their uterine fibroids. The efficacy parameters were assessment of bleeding by pictorial blood assessment chart (PBAC), fibroid volume, pain and quality of life.

The primary endpoint was the percentage of patients who were in amenorrhoea at the end of both treatment courses 1 and 2 for Part I of the study and at the end of the 4 treatment courses for Part II of the study. Amenorrhoea was defined as having no more than 1 day of spotting within a 35-day interval. All treated subjects had a diagnosis of uterine leiomyoma and all subjects had very severe uterine bleeding with a mean (median) PBAC at screening of 302 (220). The study population included was rather similar to that included in previous studies, i.e. predominantly white women, aged just above 40 years, with a Body Mass Index (BMI) of approximately 25 and the majority were of child-bearing potential. The disease characteristics were also rather similar to previous phase 3 studies, although mean PBAC, fibroid volume and uterine volume were slightly lower in this study. Surgery was

initially planned for less than 10% of the women and a small number of women (n=16, 3.5%) underwent surgery in the study.

For the primary efficacy endpoint, 62% of subjects were in amenorrhoea at the end of both treatment courses 1 and 2 in the 5 mg group. The proportion of subjects in amenorrhoea at the end of treatment course 4 was somewhat lower compared to the end of course 2. However, the proportions were considered to be of clinical relevance and 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. At the end of all 4 treatment courses, in the 5 mg group, 49 % of the women were in amenorrhoea for the FAS 1. The mean (median) PBAC scores associated with return of menstruation decreased after each subsequent treatment course.

Both fibroid volume and uterine volume decreased during the study. The total volume of the 3 largest fibroids identified at screening was shown to decrease following the first treatment course, and to further decrease after each treatment course, with no statistically significant differences identified between the two treatment groups. The mean (median) percent change from baseline (screening 3) to visit 10 was -38% (-72%) and -58% (-73%) in the PGL4001 5 mg and PGL4001 10 mg groups, respectively.

By the end of treatment course 4, 81% and 88% had a  $\geq 25\%$  uterine fibroid volume reduction in the PGL4001 5 mg and PGL4001 10 mg treatment groups, respectively. Both doses of UPA showed improvement in quality of life measurements evaluated using the specific UFS-QoL symptom severity and HRQoL scales.

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.

Thus, Esmya has been shown to be effective in reducing bleeding and anaemia as well as the size of the fibroids in women who were to undergo surgery for their fibroids. Esmya was also shown to be effective at reducing bleeding and fibroid size when used intermittently for longer periods (up to 4 treatment courses). In the long-term study with Esmya, 49% of women receiving 5 mg Esmya (95 out of the 195 women who were assessed) had no more than one day of spotting within a 35-day interval after each of the 4 treatment courses, and 70% had no more than one day of spotting within a 35-day interval at the end of treatment course 4. A reduction in fibroid size was also observed.

Bleeding often occurs in women during the premenopausal years and it is frequently associated with uterine fibroids. Uterine fibroids are the most common female pelvic tumour<sup>1</sup> and the single most common indication for hysterectomy<sup>2</sup>, a procedure that is not free of risk. The pronounced reduction of bleeding, as demonstrated during intermittent treatment with Esmya for longer periods, has the potential of substantially reducing the need for surgical removal of the uterus. The median age at menopause is 51 years with great variations. Thus, there is a natural end to the need for treatment. In patients suffering from heavy menstrual bleeding associated with uterine fibroids, repeated 3-month treatment courses with ulipristal acetate provide a medical alternative to surgery and has the potential to reduce the need for surgical intervention. There is currently no other medical alternative to surgery for treatment of moderate to severe symptoms of uterine fibroids.

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<sup>1</sup> Divakar H, 'Asymptomatic uterine fibroids', Best Pract & Research Clinical Obstetrics and Gynaecology Vol. 22(4), August 2008, pp. 643–654.

<sup>2</sup> Stewards EA, 'Uterine Fibroids', Lancet Vol. 357 (9252):, January 2001, p. 293-8..

## 2.2.2. Safety

### Potential mechanisms

The potential for a causal relationship between hepatotoxicity and the use of Esmya and possible mechanism of action is to be further investigated. From the available evidence reviewed so far, a theoretical basis risk for Drug-induced liver injury (DILI) with ulipristal acetate treatment seems fairly low.

### Literature

From a preliminary review of the existing literature, no publications were identified that would raise concerns in relation to the hepatic safety for ulipristal.

### Preclinical and Clinical trial data

The non-clinical safety of ulipristal acetate was evaluated in mice, rats, rabbits and monkeys. Overall, there are 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, in rodents and monkey.

Cumulatively, over 7,100 subjects have been exposed to at least one dose of ulipristal acetate in clinical trials, 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 various indication (including emergency contraception, uterine fibroids or healthy volunteers) and for various treatment duration. Multiple doses of ulipristal acetate have been received by 1,975 subjects, while 1,077 subjects were exposed to ulipristal acetate 5 mg/day or higher for at least one 3-month treatment course. Clinically significant abnormal liver tests for those patients were defined as laboratory values meeting Hy's Law criteria<sup>3</sup> or post-screening/baseline elevations of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) above 3 times the upper limit of normal (ULN) or total bilirubin above 2 times the ULN.

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

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 regarding liver impairment concerned levels of ALT/AST/ Gamma-Glutamyl Transferase (GGT)/alkaline phosphatase (ALP) above 2 times the 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.

In those phase II studies, no adverse events related to liver disorders were reported, and no abnormal values were noted, except for the study CDB 2914/2-A. In this Japanese study, three subjects experienced liver disorders, such as hepatic steatosis and abnormal hepatic function; however, the level of ALT/AST was never above 3 times the ULN and bilirubin was never found to be above 2 times ULN. Liver disorders detected in this study do not seem to be related with Esmya use.

In total about 1500 patients have been included in phase III clinical trials; those patients were exposed to 5 or 10 mg of ulipristal acetate, for up to 8 multiple three-month courses. Patients with ALT/AST/ALP/GGT/bilirubin above 2 times ULN (PGL07-021, PGL07-022, PGL09-026 and its extensions, PGL11-006), ALT/AST/ALP/bilirubin above or equal to 2 times ULN (PGL-W-1309, PGL-W-1208) or alcohol abusers, were excluded from phase III clinical trials.

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<sup>3</sup> FDA , 'Guideline on Drug-Induced Liver Injury: Premarketing Clinical Evaluation', July 2009

Four hepatic disorders were reported. The first was an isolated increase of GGT to 3 times the ULN at a single visit. No other hepatic laboratory values were abnormal during the 13 weeks treatment or at up to 6 month follow-up. The second 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. The fourth patient had a medical history of hepatic hemangioma and underwent hepatic hemangioma embolization during the study period. Overall, none of these cases raise concerns in relation to potential effects of ulipristal.

In the Phase III program, no case was identified having laboratory values that would meet Hy's Law criteria. There were 7 subjects with ALT above 3 times the ULN and bilirubin below or equal to 2 times the ULN, 4 subjects with bilirubin above 2 times ULN and ALT below or equal to 3 times the ULN. Out of these 11 subjects, 9 had confounding factors and for 2 subjects the increased values occurred at the follow-up 3 or 6 months visits only.

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 serious events were identified that would raise particular concern with respect to liver toxicity associated with the use of ulipristal in clinical trials settings. However, it is of note that both in the phase II and III program, patients who were alcohol abusers or had abnormal hepatic lab parameters were excluded (in most studies ALT/AST/ALP/bilirubin above or equal to 2 times the ULN). Thus, there is no experience from clinical trials on the use of ulipristal in patients with pre-existing hepatic disorders.

#### **Post marketing safety data**

A review of post-marketing safety data associated with the use of Esmya has been carried using the Standardised MedDRA Query (SMQ) 'Hepatic disorders' as well as Preferred Term 'Liver transplantation'.

Cumulatively, 68 AEs were identified. Of those, 24 were serious. Those AEs were identified from 51 cases, among which 17 were serious and 34 non-serious. For 38 of these cases there was insufficient information for a reasonable causality assessment. For 8 cases, a causal role for Esmya was not supported by the available information. There were 6 cases where the correlation with the use of Esmya could be assessed. These are summarised in Table 1 below.

Table 1

Case	Age (yrs)	MedDRA SMQ PT  TTO	Relevant medical history	Past/concomitant medication	Case description	MAH causality assessment	Rapporteur comment
1	55	Hepatic failure  109 days on Esmya	Non-smoker, No alcohol abuse, No drug allergy, Hepatitis A at age 18, Endometriosis, Adenomyosis, Actinomyces infection in Jan after IUD treated with amoxicillin, 6 months prior to the event: labs within normal range	Amoxicillin in January, Cefuroxime 750 mg from October 2014 for Klebsiella pneumoniae for 2 days (discontinued)  Sleep and Go dietary supplement in October 2014 for 2 days	Esmya: July 2014 – October 2014. From 2 <sup>nd</sup> day of treatment: fatigue, asthenia, anorexia and post-prandial fullness, no jaundice. October 2014: dysuria and micturition, Klebsiella pneumoniae in urine. October-November 2014: hospitalised due to acute hepatitis. Esmya discontinued. CA-125: 56. October 2014: 1 <sup>st</sup> day: ALT 1920 U/L, AST 1443 U/L, GGT 56 U/L, ALP 124 U/L. ALTxULN/ ALPxULN ratio ~50 (no normal ranges were provided). 2 <sup>nd</sup> day: ALT 1635 U/L, AST 1457 U/L. 3 <sup>rd</sup> day: ALT 1921 U/L, AST 1727 U/L. 4 <sup>th</sup> day: ALT 1958 U/L, AST 1794 U/L. 5 <sup>th</sup> day: ALT 1863 U/L, AST 1580 U/L. Total bilirubin 1.8 mg/dL. New hospitalisation in Nov 2014 due to unspecified hepatic profile aggregation. In November 2014, ultrasound: probable hepatic steatosis.  Serology: hepatitis virus A, B, C and E negative (except positive IgG and negative IgM for hepatitis A virus from the past), HIV 1 and 2	Confounding factors: symptoms on 2 <sup>nd</sup> day on Esmya were non-liver specific (also submucosal myomas' non-specific symptoms), urine tract infection, cefuroxime (unusually discontinued after 2 <sup>nd</sup> day, LiverTox), dietary supplement (García-Cortés 2016), first liver tests only 3 days after cefuroxime start, missing data between November and December 2014, missing serology results for CMV, EBV and herpes viruses, suspected jaundice >1 month after Esmya discontinuation, suspected steatosis, missing pathology report of explanted liver, but autoimmune hepatitis unlikely.  Liver injury type (based on ALTxULN/ ALPxULN ratio): hepatocellular. Pattern of injury: sub-fulminant hepatitis. RUCAM score: unlikely. DILIN score: low possible role. Appendix 3 and 4	No alcohol or substance abuse. Viral hepatitis and autoimmune hepatitis excluded  No information about explanted liver  MAH's confounding factors including concomitant medications not agreed.  TTO plausible  Causal role for Esmya not possible to conclude on. Some support by case description; but remaining uncertainty regarding potential confounding.

Case	Age (yrs)	MedDRA SMQ PT TTO	Relevant medical history	Past/concomitant medication	Case description	MAH causality assessment	Rapporteur comment
					<p>negatives, ANA autoimmunity, anti-ds-DNA antibodies, anti-LKM antibodies, AMA, ASMA and c-ANCA negatives; normal classes of IgG; protein electrophoresis, without monoclonal peaks; albumin 3.4 g/dL; ceruloplasmin and alpha-anti-trypsin without alterations; microbiology test (blood and urine) negative.</p> <p>In December 2014: ALT 1107 U/L, AST 1518 U/L, total bilirubin 15.35 mg/dL, GGT 80 U/L, ALP 141 U/L.</p> <p>In December 2014: total bilirubin 20.5 mg/dL, MELD score 28.</p> <p>In December 2014: total bilirubin 24.8 mg/dL (direct 14.9 mg/dL).</p> <p>In December 2014: INR 2.6, GGT 51 U/L, ALP 120 U/L.</p> <p>In December 2014: liver transplant.</p>	<p>Esmya role could neither be ruled out nor confirmed, due to confounding factors.</p>	
2	58	Autoimmune hepatitis, Drug-induced liver injury, Hepatic cirrhosis ~2	In 2014, normal lab test results, No known autoimmune disease, Renal insufficiency, No homeopathic	Aprovel (irbesartan) at beginning of 2016 for 1 month, Omeprazole February 2017	<p>Esmya: December 2016-February 2017.</p> <p>February 2017: fatigue, nausea, digestive discomfort.</p> <p>In February 2017, Esmya discontinued due to symptoms and omeprazole 10 mg daily introduced.</p> <p>In February 2017, symptoms worsened, omeprazole discontinued, ALT 2206 U/L (66.8xULN), AST 1592 U/L (49.7xULN), GGT 332 U/L (8.3xULN), ALP 146 U/L, CRP 9 mg/L,</p>	<p>Confounding factors: fatigue and digestive discomfort (also non-specific symptoms of myoma), no labs data from 7 Feb 2017 at Esmya discontinuation), omeprazole (LiverTox, El-Matary 2005, Koury 1998, Garrido 2007) for 7 days till first labs available, cirrhosis and autoimmune hepatitis signs in the</p>	<p>Some data suggestive of underlying chronic hepatic condition, e.g. due to cirrhosis in explanted liver. Unspecific test for autoimmunity positive.</p> <p>MAH's confounding factors: fatigue, discomfort, no labs, omeprazole not agreed.</p> <p>Causal role for Esmya in</p>

Case	Age (yrs)	MedDRA SMQ PT TTO	Relevant medical history	Past/concomitant medication	Case description	MAH causality assessment	Rapporteur comment
		months	products use, Hypertension, Hepatitis A with jaundice at age 7, Varicella at age 19, No alcohol abuse, Raynaud's disease		<p>no bilirubin value, ALTxULN/ ALPxULN ratio 60.7.</p> <p>In February 2017: jaundice started.</p> <p>In February 2017: jaundice, leg oedema, laminated gallbladder wall thickening with slight hyperaemia, ALT 1652 U/L, AST 1394 U/L, GGT 252 U/L, total bilirubin 436 umol/L (20.8xULN), total IgG 11 g/L, INR 2.49, EBV (positive antibody IgG, previous infection), hepatitis A positive virus</p> <p>(antibody IgG and IgM), hepatitis B and C virus negative, no sign of hepatic encephalopathy.</p> <p>In February 2017: EBV, herpes simplex positive (IgG), hepatitis B (DNA), C (RNA), E (RNA) negative, CMV (RNA, IgG and IgM), herpes (DNA) by polymerase chain reaction also negative,</p> <p>auto-antibodies positive for anti-nuclear antibodies 1/160, and negative for anti-smooth muscle, anti-LKM1, anti-cytosol, anti-DNA, anti-mitochondria, for anti-neutrophil cytoplasmic</p> <p>antibody (ANCA) and slightly elevated anti-saccharomyces cerevisiae antibody (ASCA) of 11 U/mL (normal range &lt;10), and brain natriuretic peptide was 26 ng/L.</p> <p>Tazocilline (pireacillin sodium/tazobactam sodium), N-Acetyl-cysteine and acyclovir introduced.</p>	<p>background.</p> <p>Liver injury type (based on ALTxULN/ ALPxULN ratio): hepatocellular.</p> <p>Pattern of injury: acute liver failure.</p> <p>RUCAM score: unlikely.</p> <p>DILIN score: low possible role.</p> <p>Appendix 3 and 4</p> <p>Esmya role could neither be ruled out nor confirmed, due to confounding factors.</p>	development of acute-on-chronic hepatitis not possible to conclude on. Some support by case description; but remaining uncertainty regarding potential confounding

Case	Age (yrs)	MedDRA SMQ PT TTO	Relevant medical history	Past/concomitant medication	Case description	MAH causality assessment	Rapporteur comment
					<p>In February 2017: jaundice worsening, ALT 928 U/L, AST 779 U/L, ALP 180 U/L, GGT 137 U/L, total bilirubin 571 umol/L, INR 3.0, CRP 7.9 mg/L, MELD score 36.</p> <p>In February 2017, negative HIV antibodies, anti-hepatitis C virus antibodies, hepatitis B (HBs Ag, anti-HBc), hepatitis C and hepatitis E (anti-hepatitis E virus IgM).</p> <p>In March 2017, abdominal pain, slight hepatic encephalopathy.</p> <p>In March 2017: liver transplantation.</p> <p>Explanted liver report: atrophic liver (716 gr) with marked fibrosis and pattern of cirrhosis, severe medio- and centrilobular necrosis associated with cholestasis and a massive polymorphous infiltration by inflammatory cells including lymphocytes, polynuclear neutrophils, and eosinophils and Mallory bodies. Autoimmune test: anti-nuclear antibodies at 1/10 in immunofluorescence.</p> <p>In August 2017, due to epigastric pain and mild rectorrhagia, an endoscopy: no particular abnormalities and no sign of colitis, 'internal congestive haemorrhoids' explaining mild rectal bleeding. Prednisolone discontinued, but later re-introduced.</p> <p>In October 2017, biliary stent change and in November 2017 patient doing well, receiving</p>		

Case	Age (yrs)	MedDRA SMQ PT TTO	Relevant medical history	Past/concomitant medication	Case description	MAH causality assessment	Rapporteur comment	
					also amlodipine for hypertension.			
3	45	Hepatocellular injury, Drug-induced liver injury 3-26 days on Esmya	BMI: 28.1, EBV, CMV, Herpes virus 6a and 6b in genome, No herbal products, No other drugs, No holidays abroad, No alcohol abuse	None	<p>Esmya: June 2017-July 2017.</p> <p>On 3<sup>rd</sup> day: asthenia, nausea and vomiting.</p> <p>In July 2017: jaundice, ALT 1611 U/L (46xULN), AST 1322 U/L (37.8xULN), GGT 9.4xULN; ALP 2.4xULN, total bilirubin 18xULN, ALTxULN/ ALPxULN ratio 19.9, negative for hepatitis A, B and C virus, and cytomegalovirus. A liver biopsy non-typical for drug-induced hepatitis.</p> <p>Esmya discontinued.</p> <p>In July 2017 hospitalisation, ALT 25.4xULN, AST 32.3xULN, GGT 6.3xULN, ALP 1.9xULN, total bilirubin 21.1xULN, negative for HIV 1 and 2, human T-cell lymphotropic virus 1 and 2, hepatitis B, C and E virus. PCR negative for herpes simplex virus 1 and 2, adenovirus, CMV, hepatitis virus E, but positive for human herpes virus 6A and B.</p> <p>Also, past infection EBV, CMV and VZV, and negative for autoantibodies: antinuclear, smooth muscle, liver-kidney microsomal type 1, liver-cytosol type 1, mitochondria.</p> <p>In July 2017, liver biopsy: predominant peri-portal necrosis.</p> <p>In August 2017, ALT 24xULN, AST 32xULN, total bilirubin 28.4xULN.</p> <p>In August 2017, liver transplantation.</p> <p>Explanted liver: atrophic with massive necrosis</p>	None	<p>Confounding factors: early non-specific symptoms on 3<sup>rd</sup> day (also non-specific myomas' symptoms), atrophic liver suggesting chronic underlying hepatic disease and HHV6 in genome phenomenon (Pantry 2017), early onset.</p> <p>Liver injury type (based on ALTxULN/ ALPxULN ratio): hepatocellular.</p> <p>Pattern of injury: acute/ sub-fulminant liver injury.</p> <p>RUCAM score: unlikely/possible.</p> <p>DILIN score: possible role.</p> <p>Appendix 3 and 4</p> <p>Esmya role remains possible despite confounding factors.</p>	<p>Acute viral hepatitis and autoimmune hepatitis excluded</p> <p>No concomitant medication</p> <p>Plausible TTO</p> <p>No information on alcohol use</p> <p>The finding of an atrophic liver suggests presence of a more chronic underlying hepatic condition, although no cirrhosis reported from explanted liver of medical history.</p> <p>MAH's confounding factors : non-specific symptoms, atrophic liver, early onset not agreed.</p> <p>Although no obvious confounding factors are reported in this case, the finding of an atrophic liver suggests involvement of other possible aetiology, given the relatively short time to onset</p>

Case	Age (yrs)	MedDRA SMQ PT TTO	Relevant medical history	Past/concomitant medication	Case description	MAH causality assessment	Rapporteur comment
					and lymphocyte infiltration and cholestasis.		(53 days of Esmya treatment).  Role of Esmya in the development of acute hepatitis possible but uncertainties remain.
4	38	Autoimmune hepatitis, Acute hepatic failure, Liver injury, Drug-induced liver injury  ~2.5 months on Esmya (74 tablets)	No alcohol abuse, No holidays abroad, Weakness since Jan 2016, No liver issues, Metamizole allergy?	Femigo (oestradiol, levonorgestrel) in the past, Ibuprofen October-December 2016, Ortoton (methocarbamol), Pantoprazole, Carmethin (peppermint oil and caraway oil), Azithromycin	Esmya: November 2016 - January 2017. In December 2016, a flu was treated with azithromycin for three days. In December 2016, ibuprofen discontinued due to bloody urine. On unspecified day, constipation treated with Dulcolax and Microlax, also tiredness, Navalgin was discontinued and Korodin was introduced in January 2017 for two days. In January 2017, bloody urine resolved. On unspecified date, upper abdominal disorder and in January 2017, Esmya and other treatments discontinued. In January 2017, jaundice. Two days later, hospitalisation due to increased transaminases, ALT 5558 U/L (163.5xULN), AST 3962 U/L (127.8xULN), ALP 252 U/L (2.4xULN), GGT 477 U/L (12.6xULN), total bilirubin 239 umol/L (11.4xULN), ALTxULN/ALPxULN ratio 68.1, no portal hypertension or	Despite being reported as acute liver failure, the MAH considers that this is actually a case of severe acute liver injury.  Confounding factors: azithromycin, high IgG/IgM, rapid response to prednisolone, liver biopsy result consistent with autoimmune hepatitis, auto-antibodies.  Liver injury type (based on ALTxULN/ALPxULN ratio): hepatocellular.  Pattern of injury: acute hepatocellular injury.  RUCAM score: unlikely.  DILIN score: unlikely role.  Appendix 3  Esmya role unlikely due to diagnosis of autoimmune	Acute liver failure diagnosed as likely autoimmune hepatitis, based on pathology but not well supported by antibody pattern. Also supported by response to steroid.  The MAH argument that this is an 'acute liver injury' but not an 'acute liver failure' questionable; transplantation was considered, but since she responded to steroid treatment not thereafter needed.  Ibuprofen not considered a likely cause.  Causal role for Esmya supported by the case description but uncertainty remains regarding potential autoimmunity.

Case	Age (yrs)	MedDRA SMQ PT TTO	Relevant medical history	Past/concomitant medication	Case description	MAH causality assessment	Rapporteur comment
				<p>December 2016 (3 days), Novalgin (metamizole drops) from December 2016, Dulcolax (bisacodyl suppositories), Microlax (dodecyl sodium citrate and sorbitol rectal solution), Korodin (camphor) January 2017</p>	<p>ascites. In January 2017, ALT 126.6xULN, AST 92.2xULN, ALP 2.0xULN, GGT 10.3xULN, total bilirubin 10.3xULN. In January 2017, two days later: ALT 139.4xULN, AST 104.5xULN, ALP 1.7xULN, GGT 8.7xULN, total bilirubin 13.7xULN. In January 2017, IgG 18.2 g/L (normal≤16.0), IgM 5.56 g/L (normal≤2.3). CMV, EBV, VZV, herpes simplex, hepatitis A, B, C, E tests were negative. Patient clinically stable and not listed for transplantation. In January 2017, liver biopsy: confluent lobule-centered, partially bridging liver epithelial necrosis with moderate lobular and (peri) portal inflammation with plasma cell proliferation and liver cell rosettes, without fibrosis, consistent with severe autoimmune hepatitis. Prednisolone, vitamin K, L-ornithine and Bifiteral were introduced. In January 2017, serum diff.AMA: aPDH-E2 and AMA M2 tests positive. In February 2017, ALT 34.1xULN, AST 10.7xULN, ALP 1.5xULN, GGT 16.2xULN, total bilirubin 6.4xULN. In February 2017, discharged with diagnosis of autoimmune hepatitis responding to steroid. However, auto-antibodies did not show a typical pattern for autoimmune hepatitis.</p>	hepatitis.	

Case	Age (yrs)	MedDRA SMQ PT TTO	Relevant medical history	Past/concomitant medication	Case description	MAH causality assessment	Rapporteur comment
					<p>As the patient improved rapidly on steroid, the indication of liver transplantation, initially considered, was not confirmed</p> <p>In February 2017, ALT 383 U/L (10.9xULN), AST 123 U/L (3.5xULN), IgA of 0.64 g/L (0.9xLLN), IgM of 3.19 g/L (1.4xULN), ALP 109 U/L (1.0xULN), GGT 287 U/L (7.2xULN).</p> <p>In February 22017, seven days later: ALT 148 U/L, AST 52 U/L, ALP 65 U/L, GGT 140 U/L.</p> <p>In June 2017, ALT 48 U/L (1.4xULN), AST 37 U/L (1.2xULN), ALP 38 U/L, GGT 32 U/L, total bilirubin 5 umol/L.</p>		
5	54	Drug-induced liver injury ~end of Fibrystal 3-month course	Penicillin allergy	Vitamin D, Vitamin B Complex, Ibuprofen	<p>Fibrystal: October 2016 -February 2017.</p> <p>In January 2017, flu (myalgia, weakness), resolved few days later.</p> <p>Unspecified date: decreased appetite, fatigue, jaundice, dark urine and weight loss.</p> <p>In February 2017, ALT 1996 U/L (36.3xULN), ALP 112 U/L (1.1xULN), bilirubin 60 umol/L (2.7xULN), GGT 173 U/L (3.5xULN).</p> <p>In February 2017, the day after: ALT 1916 U/L, AST 1039 U/L (28.9xULN), ALP 125 U/L, bilirubin 52 umol/L, GGT 178 U/L, IgA 3.96 g/L (normal &lt; 3.00 g/L).</p> <p>Abdominal ultrasound: liver at the upper limits of normal: 15.8 cm, mildly coarsened liver echotexture.</p>	<p>Confounding factors: flu, continuously increased IgA (Gonzalez-Quintela 2007), missing information on alcohol abuse, missing serology test results for viruses or autoimmune hepatitis.</p> <p>Esmya role not supported due to confounding factors.</p>	<p>Case reported as Drug-induced liver injury (DILI) after 3.5-4.5 months of Esmya treatment. Repeated liver lab parameters at and after (weekly for 6 weeks) ulipristal discontinuation showed steady reduction of high levels of ALT, AST, bilirubin and GGT.</p> <p>MAH's confounding factors vitamins, ibuprofen not agreed.</p> <p>Lab data from 6 Mar-17 may suggest autoimmune components. Unknown if patient</p>

Case	Age (yrs)	MedDRA SMQ PT TTO	Relevant medical history	Past/concomitant medication	Case description	MAH causality assessment	Rapporteur comment
					<p>Fibrystal discontinued on in February 2017.</p> <p>In February 2017, no jaundice.</p> <p>In February 2017, ALT 1677 U/L, AST 805 U/L, ALP 125 U/L, bilirubin 70 umol/L, GGT 232 U/L.</p> <p>In February 2017, ALT 839 U/L, AST 414 U/L, bilirubin 59 umol/L, GGT 196 U/L.</p> <p>In March 2017, ALT 703 U/L, AST 382 U/L, bilirubin 53 umol/L, GGT 200 U/L, IgA 4.25 g/L.</p> <p>In March 2017, positive smooth muscle antibody with smooth muscle antibody titre of 1:80 (ULN: 1:20).</p> <p>In March 2017, ALT 85 U/L., AST 51 U/L, GGT 71 U/L.</p> <p>In March 2017, a week later, ALT 68 U/L, AST 50 U/L, GGT 60 U/L IgA 4.46 g/L.</p> <p>In August 2017, IgA 3.73 g/L.</p> <p>In Sep 2017, incidental cardiac murmur.</p>		<p>received steroid treatment</p> <p>Available data limited. No strong alternative explanation reported. Dechallenge in terms of increased liver lab parameters observed</p> <p>Some support for causal relationship between Esmya and liver injury but uncertainty due to missing information.</p>
6	48	Hepatic necrosis 10 days on Fibrystal second course	Post-menopausal	Oestrogen (for menopause)	<p>Fibrystal dates unknown.</p> <p>On 10<sup>th</sup> day of second course: nausea, abdominal pain, extreme fatigue and jaundice, transaminase about 2500, increased INR and bilirubin.</p> <p>Fibrystal discontinued.</p> <p>Liver biopsy: necrotising idiopathic hepatitis.</p> <p>Few months later, recovered.</p> <p>Unspecified date, diagnosis of Sjögren's</p>	<p>Confounding factors: early appearance in second course, oestrogen (LiverTox), Sjögren's syndrome, missing exact results of viral and autoimmune hepatitis investigations.</p> <p>Esmya role not supported due to confounding factors.</p>	<p>More information obtained since LEG 19 procedure.</p> <p>Limited information.</p> <p>MAH's confounding factors agreed. Acknowledged that Sjögren's syndrome may have liver manifestations, but a hepatic necrosis is unlikely, and there is uncertainty about the</p>

Case	Age (yrs)	MedDRA SMQ PT TTO	Relevant medical history	Past/concomitant medication	Case description	MAH causality assessment	Rapporteur comment
					<p>syndrome. Unspecified virus and autoimmune tests negative.</p>		<p>diagnosis including time relationship with hepatic necrosis and Esmya treatment.</p> <p>MAH describes early appearance in 2<sup>nd</sup> course of Esmya treatment as confounding factor. In an immune-allergic reaction, early appearance of liver injury when beginning second course of treatment not unlikely</p> <p>Appears that after ulipristal was discontinued, liver biopsy suggested necrotizing idiopathic hepatitis, which a few months later recovered.</p> <p>Despite possible confounding and missing information; case of positive dechallenge, and a possible causal role of Esmya.</p>

For two of the above cases of liver failure (case 1 and case 2), there is insufficient information to either conclude or disregard a causal relationship with Esmya.

The first case concerns a 55-year old patient starting Esmya treatment for uterine fibroids with menometrorrhagia. Esmya was taken for 109 days, which is longer than the recommended 3 month treatment course. Liver transplant occurred 49 days after the interruption of the treatment with Esmya. Fatigue, asthenia, anorexia and post-prandial fullness were reported 2 days after start of the treatment; no additional information analysis on these events is available, therefore it is not clear if they could be early symptoms of hepatitis. The short time to onset suggests an ongoing condition; however, there is no information in the patient's anamnesis and medication history that would justify these events as related to hepatic injury. Hepatitis was reported with a time to onset of 109 days. The patient did not suffer from viral and autoimmune hepatitis. Therefore, the role of Esmya in the hepatic impairment of the patient could neither be excluded nor confirmed.

The second case concerns a 58 year old patient starting Esmya treatment for uterine fibroids with frequent bleeding. The patient did not use alcohol and had no substance abuse. Medical history included a past infection with hepatitis A virus with complete recovery and varicella virus; it is not suggestive of autoimmune disorders.

After approximately 2 months of treatment with Esmya, the patient suffered from fatigue and nausea and interrupted the treatment. The liver condition of the patient became progressively worse afterwards. Acute liver failure occurred 4 weeks after stopping Esmya. The patient was subject to liver transplantation. Pathological examination of the explanted liver suggested an underlying chronic hepatic condition due to pre-existing liver cirrhosis which might lead to a higher risk for severe Drug-induced liver injury (DILI)<sup>4</sup> and with signs of acute necrotising hepatitis. A viral aetiology was ruled out. There were no indications of autoimmune disease in the medical history of the patient, the anti-nuclear antibodies were found to be positive. Although this finding is unspecific, an autoimmune cause for the chronic and acute lesions could be possible. Therefore, Esmya role in the development of acute liver failure could neither be ruled out nor confirmed, due to confounding factors.

For one case of liver transplant reported (case 3), there could be a causal relationship with Esmya. This case concerns a 45-year old patient starting Esmya treatment for uterine fibroids with menorrhagia. Medical history included past Epstein-Barr virus (EBV) infection. The patient did not take concomitant medications. At 53 days after the first dose of Esmya, the patient experienced nausea, weight gain and asthenia, and Esmya was discontinued due to these events. Two days later, the patient presented jaundice and increased hepatic enzymes. The patient thereafter worsened, having fulminant hepatitis resulting in liver transplantation about 4 weeks after Esmya discontinuation. Viral hepatitis (including HHV6 a/b) could not be ruled out. The explanted liver was atrophic. Although no obvious confounding factors are reported in this case, the finding of an atrophic liver suggests involvement of other possible aetiology, given the relatively short time to onset (53 days of Esmya treatment). Therefore, the role of Esmya in the development of acute hepatitis in this patient is possible, but uncertainties remain.

Case 4 concerns a 38-year old patient being treated with Esmya for uterine fibroids. The patient had no previous liver problems, no relevant previous disease or chronic infection. The patient had an estimated exposure to Esmya of 53 - 84 days, and was hospitalized five days after the interruption of the treatment due to acute hepatitis. Liver transplantation was initially indicated, but could be avoided due to a good response to treatment with prednisone.

Viral hepatitis was ruled out. The findings of the liver biopsy indicated autoimmune disease as the most likely diagnosis. However, the measurement of auto-antibodies did not show a typical pattern of

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<sup>4</sup> Chalasani N., Bonkovsky HL, Fontana R., Lee W., Stolz A. et al., 'Features and Outcomes of 899 Patients with Drug-induced Liver Injury: The DILIN Prospective Study', *Gastroenterology* Vol. 148(7):, June 2015 , p. 1340–1352.e7.

autoimmune hepatitis. Therefore, a causal role for Esmya is supported by the case description but uncertainty remains regarding potential autoimmunity as alternative etiology.

In addition, there are two other cases, where a role of Esmya is possible, and where additional information has become available. One represents a positive de-challenge case (case 5), based on data of liver lab parameters from at least 6 weekly repeated measurements, which shows a steady normalisation of enhanced hepatic enzyme levels as well as bilirubin and GGT, following Esmya discontinuation. No other reasonable explanation for these liver effects, beyond Esmya, is evident.

The other case (case 6) was a reported hepatic necrosis, where on the 10<sup>th</sup> day of the second Esmya course, the patient reported nausea, abdominal pain, extreme fatigue and jaundice, transaminase about 2500, increased international normalized ratio (INR) and bilirubin. Ulipristal was discontinued. A liver biopsy showed necrotising idiopathic hepatitis, which a few months later recovered. At an unspecified date, the patient had a diagnosis of Sjögren's syndrome. 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. Taken together, this is not a strong case, but data could point to a positive de-challenge, and a possible causal role of Esmya.

During the review of the cases described above, a spontaneous case was reported regarding an acute liver failure associated with the use of Esmya. The case has been reported on January 30<sup>th</sup>, 2018, and concerns a 46 years old patient suffering from uterus myomatosis accompanied by menorrhagia. The patient was vaccinated against hepatitis A and B. Liver tests were performed and normal before treatment but no tests was performed during Esmya treatment. She was treated with Esmya for 6 months (it is unclear whether there was any treatment interruption). After 10 days from the interruption of the treatment the patient reported weakness and loss of appetite. Her conditions got worse in the forthcoming days, with the development of icterus, drowsiness, generalized rash with localized itching. The patient was hospitalized 20 days after the interruption of Esmya treatment.

At day of hospitalization the liver function test shows enhanced hepatic values (GOT 2614 U/l; GPT 1653 U/l; bilirubin 31.1 mg/dl; INR 3.4). There were no signs of autoimmune hepatitis or Wilson disease. The hepatitis serology was negative except for Hepatitis E IgM which was positive. However, HEV-RNA was not detected in faeces. Biopsy showed damage of liver tissue (hepatic type) accompanied by signs of collapse, portal and septa-building fibrosis with beginning dearrangement of the architecture. In addition, mild parenchymatous steatosis was detected. Due to histologic results a medicinal or toxic noxious agent was suspected first line as causing the observed liver damage. The patient developed hepatic encephalopathy, bilirubin 21.1 mg/dl, INR>7 in line with progressive liver failure. The patient was subject to liver transplantation. 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. For this case there are still uncertainties due to lack of information, such as a missing pathology report of the explanted liver and regarding confounding factors. Due to the limited information gathered so far, no firm conclusion can be drawn at this stage that would demonstrate or not the causal relationship of Esmya with the incidence of liver failure for this patient.

PRAC also noted cases of patients with a pre-existing hepatic impairment who were treated with Esmya and whose condition has not worsened.

### 3. 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.

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 therapeutic indication for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age was 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. In patients suffering from heavy menstrual bleeding associated with uterine fibroids, repeated 3-month treatment courses with ulipristal acetate provide a medical alternative to surgery and have the potential to reduce the need for surgical intervention.

PRAC reviewed all data currently available from post-marketing settings and from clinical trials as well as the responses provided by the marketing authorisation holder on cases of serious liver injury reported with Esmya. In addition to these, a preliminary assessment of a recently reported case of liver transplantation with fatal outcome was performed. Follow-up information on this case was also reviewed by the PRAC, as well as additional information provided by the Marketing Authorisation Holder while the review was ongoing.

No signal of hepatic toxicity was identified during the review of non-clinical or clinical trials of Esmya inducing hepatic toxicity. The absence of findings in clinical trials has to be interpreted with caution as abnormal values of ALT/AST was an exclusion criterion *as per* protocols

In post-marketing settings, a total of four cases of acute liver failure leading to liver transplantation including one with fatal outcome have been reported in patients exposed to Esmya. In addition, several cases of hepatic injury in patients using Esmya were reported. The impact of the new safety findings in the currently authorised indications of Esmya cannot be evaluated with certainty at present in view of the limited data available. An in depth assessment is needed to firmly establish factors that may have caused the reported serious hepatic injuries. It is therefore too early to conclude that the risk of hepatotoxicity is associated with the use of Esmya for all cases. However, there are a few cases of serious hepatic injury, where no other obvious explanation has been identified, despite uncertainty in relation to possible confounding. Among those, there are positive de-challenge cases. In addition, PRAC considers that involvement of Esmya in at least two of the four transplantation cases reported and in two additional less serious cases, is at least plausible. Nevertheless, the review of cumulatively reported post-marketing cases does not allow a firm conclusion at this stage. Even though it is unclear at this stage whether monitoring of transaminases would necessarily prevent further severe cases, liver function monitoring is expected to be an important measure to detect liver injury during treatment, and likely reduce the incidence of severe cases.

Given the estimated exposure to Esmya of approximately 175,000 patient years, the number of cases of subacute severe liver impairment leading to liver transplantation with Esmya is higher than expected (4 transplantation cases among 175,000 patient years - a total of 7 cases with severe liver impairment among 175,000 patient years; although causality is uncertain for some of these cases).

Although firm conclusions cannot be drawn that these cases were caused by Esmya, the available data raise serious concerns. While the magnitude and nature (e.g. pattern of hepatotoxicity and possible mechanism of action) of the risk are being reviewed in depth, having considered the seriousness of the

risk, the PRAC considered that the above raised a reasonable doubt that justifies adopting provisional measures in the meantime.

The PRAC considered the potential risk of hepatotoxicity of the product, together with the fact that Esmya is a symptomatic treatment and not curative, that has the potential to reduce the need for surgical intervention. The PRAC considered the duration of treatment with Esmya, the timelines of the current scientific evaluation and the patients that are currently under treatment. Considering all these factors, in order to recommend the measure that would be the most proportionate, the PRAC concluded to provisionally limit the use of the medicinal product to patients that are currently under therapeutic treatment. With regards to patients under intermittent treatment, the use of the medicinal product should not be repeated in patients who have finalised a previous treatment course. In addition, for patients currently under treatment, a monitoring of serum transaminases levels should be performed at least monthly and immediately in case of incidence of signs and symptoms of liver injury. Patients exhibiting signs and symptoms suggestive of liver injury should promptly contact a healthcare professional. Liver monitoring should also be performed up to four weeks after the discontinuation of the treatment. Healthcare Professionals (HCPs) should be informed of the cases of liver injury and hepatic failure reported with the use of Esmya in post-marketing experience. The threshold of transaminases elevation for patients not included in clinical trials, which is two times the upper limit of normal, should be considered as the threshold in which the discontinuation of treatment is recommended. Patients overcoming such threshold should be closely monitored after discontinuation of the treatment.

The above provisional measures should be reflected in the terms of the marketing authorisation, including the product information of Esmya, and communicated to HCPs via a DHPC. The adequacy of these provisional measures will be reviewed as part of the ongoing Article 20.

## **4. Risk management**

The Committee considered the proposals for risk management submitted by the MAH. Although it is not possible to draw firm conclusions that the cases reported are caused by Esmya, the available data raise serious concerns.

Having considered the risk minimisation measures proposed by the MAH, the PRAC considered that they are not able to sufficiently reduce the risks to an acceptable level.

The PRAC recommends the following provisional measures to be implemented awaiting the outcome of the scientific evaluation.

### ***4.1. Conditions with regard to the safe and effective use of the medicinal product***

PRAC recommends that no new patients should be treated with the medicinal product while the review under Article 20 of Regulation (EC) No 726/2004 is ongoing. With regards to patients under intermittent treatment, the use of the medicinal product should not be repeated in patients who have finalised a previous treatment course.

### ***4.2. Amendments to the product information***

The PRAC considered that temporary risk minimisation measures in the form of updates to the product information would be necessary in order to minimise the risk associated with the use of Esmya, until a thorough assessment of the available data is performed. These changes include amendments to sections 4.2 and 4.4 of the SmPC. The Package Leaflet should be amended accordingly.

PRAC recommended monitoring of the liver function at least monthly for patients under treatment as well as up to four weeks after the discontinuation of the treatment. These investigations should occur immediately in case a patient shows signs or symptoms compatible with liver injury. Patients who develop transaminase levels above 2 times the upper level of normal during Esmya treatment should stop the treatment and be closely monitored.

#### ***4.3. Direct Healthcare Professional Communications and Communication plan***

The PRAC adopted a Direct Healthcare Professional Communication (DHPC) to inform healthcare professionals of the risk of liver injury and the provisional measures to limit the use and monitor patients under treatment. The PRAC also agreed on a communication plan.

## 5. 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), in particular the need for provisional measures in accordance with Article 20(3) of Regulation (EC) NO 726/2004.
- During the ongoing review of safety and efficacy data in relation to the overall risk of liver injury with Esmya, the PRAC reviewed all data currently available from post-marketing settings and from clinical trials as well as the responses provided by the marketing authorisation holder on cases of serious liver injury reported with Esmya.
- The PRAC noted that four cases of acute liver failure leading to liver transplantation including one with fatal outcome have been reported with Esmya. PRAC concluded that the use of Esmya could potentially be associated with a risk of serious liver injury. In view of the seriousness of the cases, the PRAC considered that provisional measures are now needed to minimise this risk and protect patients, while the review is ongoing and a thorough assessment of all available data related to the benefit-risk of Esmya is performed.
- The PRAC recommends that no new patients should be treated with the medicinal product while the review is ongoing. The provisional measures proposed by PRAC also include the limitation of use of the medicinal product in patients that are currently under therapeutic treatment. With regards to patients under intermittent treatment, the use of the medicinal product should be discontinued in patients who have finalised a previous treatment course.
- PRAC recommended monitoring of the liver function at least monthly of patients under treatment as well as up to four weeks after the discontinuation of the treatment. These investigations should occur immediately in case a patient shows signs or symptoms compatible with liver injury. Patients who develop transaminase levels > 2 times the upper level of normal during Esmya treatment should stop treatment and be closely monitored.
- Furthermore, 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.

In view of the above, the Committee considers that the benefit-risk balance of Esmya remains favourable subject to the agreed provisional measures.

The Committee, as a consequence, recommends the variations of the terms of the marketing authorisation for Esmya.

This recommendation is without prejudice to the final conclusions of the ongoing procedure under Article 20 of Regulation (EC) No 726/2004.