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Liver safety parameters of ulipristal acetate for the treatment of uterine fibroids: a comprehensive review of the clinical development program

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ABSTRACT

Introduction: Uterine fibroids are benign tumors within the uterine wall affecting women. Ulipristal acetate 5 mg was first authorized in the European Union on 23 February 2012, with a post-marketing exposure estimated to be more than 765,000 patients so far. During the post-marketing experience, sporadic cases of liver injury and hepatic failure were reported. A detailed review of the clinical trials carried out in the development of ulipristal acetate 5 mg was undertaken to further assess the liver safety data reported during the clinical trials.

Areas covered: A detailed review of clinical data from Phase I to Phase III of patients exposed to ulipristal acetate at any investigated dose levels and for any treatment duration was conducted and the liver function test values are presented. In addition, a literature review on drug-induced liver injury is provided

Expert opinion: The experts present an evaluation of the liver safety findings observed during the clinical development and their views on the role of these findings in predicting the occurrence of drug-induced liver injury, the benefits of the treatment, the safety and the implications to the current clinical practice.

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Drug-induced liver injury; DILI; ulipristal acetate; transaminases; bilirubin; safety

1. Introduction

Uterine fibroids (also known as myoma, leiomyoma, and fibromyoma) are benign tumors consisting of smooth muscle cells and connective tissues that grow within the uterine wall and can have serious pathological consequences for women. Uterine fibroids are the most common female pelvic tumor [1], and the single most common indication for hysterectomy [2–4]. When symptomatic, uterine fibroids cause heavy uterine bleeding, anemia, abdominal pressure, abdominal pain, increased urinary frequency, and infertility [3,4].

Traditionally, uterine fibroid treatment has been surgical. Several alternative treatments to surgery have been developed but most of these are still invasive in nature and associated with various advantages and disadvantages compared to surgery. However, a need remains for a long-term medical treatment option that may postpone surgical interventions or eliminate the need for surgery altogether [5] since some women are either ineligible or prefer to avoid surgery partially due to associated risks and/or potential impact on fertility.

Ulipristal acetate (UPA) 5 mg per day is a treatment developed specifically to treat most of the moderate to severe symptoms of uterine fibroids in adult women of reproductive age, not only pre-operative but also for longer periods of intermittent treatment in women who are not considering surgery [6].

Esmya was first authorized in the European Union on 23 February 2012. The current post-marketing exposure to Esmya is estimated to be approximately 765,000 patients. During the

post-marketing experience, 8 cases of severe liver injury were reported. The contributing role of Esmya in these cases was possible. Of these, there were a total of four cases of acute liver failure leading to liver transplantation. In May 2018, the European Medicines Agency (EMA) concluded the evaluation and recommended that several measures be put in place to minimize the risk of rare but serious liver injury with Esmya (UPA) [7]. These measures are further discussed in this article.

In view of the recent safety review on UPA, this article presents a detailed review of the clinical trials carried out in the development of UPA 5 mg which was undertaken to further assess the liver data reported during the clinical trials.

2. Methods

In order to evaluate the frequency of abnormal liver function test values, a review of clinical data from Phase I to Phase III of patients exposed to UPA at any investigated dose levels and for any treatment duration was conducted. The clinical trials reviewed are outlined below.

2.1. Criteria for evaluation of abnormal liver safety values

The evaluation was carried out according to the recently revised international definitions, characterization, criteria of severity for drug-induced liver injury (DILI) [8,9]. Acute drug-induced liver

Article highlights

- Over 1,800 subjects exposed to doses of between 2.5 and 50 mg UPA with no liver issues reported during Phase I – III
- No patients receiving 5 mg reported ALT/AST > 3×Upper Limit Normal (ULN) with no patients in any phase meeting Hy's Law criteria during long-term intermittent treatment with 5 and 10 mg UPA
- Sporadic reports of liver injury and hepatic failure reported in post-marketing environment
- The role of UPA as a potential DILI-inducing agent not confirmed
- In vitro studies or pre-clinical data of UPA did not indicate any particular risk for DILI
- No other efficacious/licensed medical alternative for long-term treatment of moderate to severe symptoms of uterine fibroids

This box summarizes key points contained in the article.

injury has been defined by biochemical criteria as follows: 1) an elevation of serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 times the upper limit of normal (ULN); 2) an elevation of serum alkaline phosphatase (ALP) >2 times the upper limit of normal; 3) the combination of ALT/AST >3×ULN and serum total bilirubin >2×ULN [8,9]. The combination of ALT/AST >3×ULN and serum total bilirubin >2×ULN, is the criterion that defines Hy's law which is derived from Hyman Zimmerman's observation [10,11] and represents a signal of a particular risk of severe liver injury [10,11]. Indeed, the presence of Hy's law cases in a clinical trial anticipates a 10% risk of liver failure and/or liver transplantation in patients with hepatocellular liver injury type (ALT × ULN/ALP×ULN >5) [11]. In Hy's law, bilirubin is considered as a liver function test to indicate functionality of the liver, after exclusion of cholestasis and an obvious cause other than DILI (e.g. obstruction of bile duct) [8–11].

Elevations of ALT 3×ULN and alkaline phosphatase (ALP) 2×ULN are rare in clinical trial populations without underlying liver disorder and can thus be considered a safety signal [12]. In placebo treated patients in clinical trials, elevation of serum ALT >3×ULN occurs in around 0.5% of subjects [13]. Furthermore, if a drug is stopped in a timely manner (i.e. as early as possible), then for most of those drugs that potentially cause liver injury, there is normally a rapid resolution of the DILI [14].

Consequently, this liver safety review of clinical trials has been based on the presence of, or a combination of ALT/AST >3×ULN, ALP >2× ULN and Hy's Law, criteria.

2.2. Data from clinical trials

Under the hypothesis that UPA could have an effect on the liver and its function, the review included clinical trials with healthy subjects and subjects with uterine fibroids including subjects treated with the marketed UPA tablet 5 mg/daily and the highest investigated multiple doses (up to 50 mg/day).

2.2.1. Phase I clinical trials

Data from reviews of Phase I clinical trials consider 176 subjects exposed to multiple daily oral doses ranging from to 2.5 to 50 mg.

The relevant trials included a clinical trial looking at pharmacokinetics (PK) and safety in healthy women, with UPA 10, 20, 50 mg daily or placebo (8 subjects in each group) for 10 consecutive days [15]. An additional clinical trial was conducted by Watson

Laboratories looking at QT/QTc interval prolongation, in healthy women taking UPA 10 mg or 50 mg daily or placebo (47 subjects in each group) for 8 consecutive days [16]. Another clinical trial was conducted with both single and multiple doses. In the single dose part, 24 subjects were exposed to 2.5, 5, 10, and 20 mg (6 subjects in each group) and 8 subjects to placebo and in the multiple dose part, 18 subjects were exposed to ulipristal acetate 2.5, 5, and 10 mg (6 subjects in each group) and 6 subjects to placebo daily for 10 days in the repeated doses part [17].

Furthermore, a clinical trial was carried out in two groups of subjects, one group with moderate hepatic impairment and one group with normal hepatic function [14]. The two groups were matched for age, weight, and tobacco use. In this trial, the PK of UPA and its main metabolite (PGL4002) was reviewed. Eight women with moderate liver dysfunction (Child-Pugh score of 7–9) [18] and eight normal hepatic function women (16 total subjects) were included. After at least 10 h overnight fasting, UPA 10 mg was administered at the scheduled time, serial blood samples for PK evaluation were collected, and safety variables assessed over the next 120 h post-administration of a single dose.

2.2.2. Phase II clinical trials

The Phase II clinical trials included 152 subjects exposed to multiple daily doses of 2.5, 5, 10, or 20 mg. In all these trials, subjects were excluded at screening if ALT/AST/gamma glutamyl-transferase (GGT)/ALP >2×ULN, if there were abnormalities (significant) in laboratory results, presence of hepatic disorders or in the case of alcohol abuse.

These clinical trials included a Phase II clinical trial [19] looking at safety and efficacy in women with uterine fibroids, one trial with UPA 10 mg (8 subjects), 20 mg (6 subjects) daily or placebo (8 subjects) for 12 weeks and another trial with UPA 10, 20 mg daily (16 subjects in each group) or placebo (13 subjects) for 12 weeks with an optional 12-week open-label extension (3 subjects in 10 mg and 6 subjects in 20 mg group) [20].

Another Phase II clinical trial was conducted, looking at the safety and efficacy (contraception) in healthy women with regular menstrual cycles of UPA 2.5, 5, and 10 mg daily (12, 12, and 11 subjects, respectively) or placebo (11 subjects) for 12 weeks [21]

Furthermore, a trial was carried out, looking at 71 subjects exposed to ulipristal acetate 2.5, 5, and 10 mg daily (23, 23, and 25, respectively), 24 to leuporelin 1.88–3.75 mg every 4 weeks, and 24 to placebo for 12 weeks [22].

2.2.3. Phase III clinical trials

The relevant exclusion criteria at screening in Phase III clinical trials included ALT/AST/ALP/GGT/bilirubin >2×ULN (PEARL I [5], PEARL II [23], PEARL III [24] and its extensions [25], PEARL IV [26]), or alcohol abusers.

During the Phase III development of UPA, several trials were conducted. The first two trials were short-term Phase III trials for registration for the indication of uterine fibroids. PEARL I [5] was a double-blind, randomized and placebo controlled trial with one 3-month treatment course of either 5, 10 mg UPA (95 and 98 subjects respectively) or placebo (48 subjects). Liver tests were measured approximately every 4–5 weeks during treatment followed by 1, 3, and 6 months follow-up visits. PEARL II [23] was

a double-blind, randomized, active comparator-controlled trial with one 3-month treatment course of either 5, 10 mg UPA (97 and 103 subjects, respectively) or leuprorelin acetate 3.75 mg (101 subjects). Liver tests were measured approximately every 4–5 weeks during treatment followed by 1, 3, and 6 months follow-up visits.

Further trials were initiated to assess the efficacy and safety of the long-term repeated intermittent administration of UPA in subjects with symptomatic fibroids [24,25]. PEARL III and its extension [24] had a trial design of open label, 3-month treatment courses (up to 4 courses in total) with UPA 10 mg (PEARL III, 209 subjects; PEARL III extension, 131 subjects), each followed by a randomized, double-blind, period of 10 days treatment with norethisterone acetate (NETA) or placebo. Liver tests were measured at screening, before starting treatment and at the 1st and 2nd month of the 1st treatment course, at the end of the 1st course, between the 1st and the 2nd course, at the end of the 2nd course, after the 3rd course, at the end of the 4th course followed by a 3 months follow-up visit. PEARL Extension 2 [25] had a trial design of 4 additional 3-month treatment courses (up to 8 courses in total) with UPA 10 mg (64 subjects). PEARL IV [26] was a double blind, randomized, long-term, intermittent trial of up to four 3-month treatment courses with UPA 5 mg (230 subjects) or 10 mg (221 subjects). Liver tests were measured at screening, the 1st and the 2nd month of 1st treatment course, at the end of the 1st course, between the 1st and the 2nd course, at the end of the 2nd course, between the 2nd and the 3rd course, at the end of the 4th course followed by a 3-month follow-up visit.

In total, during the phase III trials, 1,053 subjects were exposed to either 5 or 10 mg UPA daily, for the management of uterine fibroids during one or multiple (up to eight) 3-month treatment courses (Table 1).

2.2.4. Other studies

PREMYA, a non-interventional study, was conducted following the initial marketing authorization in February 2012 as a Post Approval Safety Study (PASS) [27]. The objective was to describe a 'real-world' medical practice for patients with uterine fibroids treated with Esmya 5 mg. In this study, a total of 1,473 patients were followed for up to 15 months (3 months treatment course and 12 months follow-up). No patient was reported with hepatic disorder SMQ AE in this study.

3. Results

A detailed review of liver tests in the Phase I, II, and III clinical trials, as well as hepatic disorders in Standardized MedDRA Queries (SMQ) related AEs was carried out. SMQs are pre-determined

sets of MedDRA terms (Preferred Terms) grouped together that relate to a defined medical condition. Hepatic disorder SMQ is broad and includes cholestasis, hepatitis, liver infections and cysts, any liver test abnormalities, etc.

In the Phase I clinical trials, with repeated daily doses up to 10-fold the marketed dose (5 mg) and up to 10 days exposure, no alterations were observed in ALT, AST, ALP, total bilirubin, and serum (GGT) and no liver disorder related adverse events (AEs) were reported for these subjects.

In the PK trial, the single dose administration of UPA 10 mg was well tolerated by both the moderately hepatic impaired subjects and the healthy control subjects. The trial results suggest no major effect of moderate hepatic impairment on the PK parameters of UPA in this group of patients classified as having moderate hepatic impairment mainly due to encephalopathy and ascites, but with no relevant impairment of metabolic function at inclusion. This trial demonstrated that UPA administered at a single dose of 10 mg, did not induce changes in the liver profile of these subjects.

In the 2 Phase II clinical trials with daily doses up to 4-fold of the marketed dose (5 mg) for 12 weeks, no liver disorder related AEs were reported. No liver test results of ALT/AST >2×ULN or total bilirubin >1.5×ULN were noted in these trials. In the Phase II trials, no subjects reported liver disorder related AEs or showed ALT/AST >1×ULN or ALP/total bilirubin >2×ULN.

3.1. Liver parameters in phase III trials

In the reviewed clinical trials, all liver results were measured against an upper limit of normal (ULN) range values. For the Phase III clinical trials, the ULN values were as follows: Aspartate Transaminase (AST) ≤37 IU/L, Alanine Aminotransferase (ALT) ≤47 IU/L, Alkaline Phosphatase (ALP) ≤135 IU/L, and Bilirubin ≤19 μmol/L. Seven subjects on 10 mg UPA had ALT or AST >3×ULN and 2 subjects on 10 mg UPA had ALT or AST values >5×ULN after administration of at least one dose of UPA. No patients taking UPA 5 mg had ALT or AST >3×ULN or above after administration of at least one dose of UPA. The number of subjects during the Phase III clinical trials with post-baseline ALT or AST >3×ULN is presented in Table 2.

3.1.1. Alanine transaminase

ALT values >3×ULN have been previously reported in 7 subjects after administration of at least one dose of UPA [28]. In summary, in the PEARL I trial (193 subjects), no subjects in the placebo group or the 5 mg group had ALT >3×ULN at any visit, however ALT >3×ULN was observed in 3 subjects in UPA

Table 1. Patients in PEARL trials per dose group.

Study/Dose	5 mg	10 mg	Total
PEARL I [5]	95	98	193
PEARL II [23]	97	103	200
PEARL III (including PIII extension and PEARL extension 2) [24,25]	0	209	209
PEARL IV [26]	230	221	451
Total	422	631	1053

PEARL Trial References 5, 23, 24, 25, 26

Table 2. ALT/AST elevations post-baseline in Phase III trials.

Laboratory value	Placebo	Ulipristal Acetate	Ulipristal Acetate	Ulipristal Acetate
	(N = 48) n (%)	5 mg (N = 422) n (%)	10 mg (N = 631) n (%)	Total (N = 1053) n (%)
ALT or AST >3×ULN	0	0	7 (1.1)	7 (0.7)
ALT or AST >5×ULN	0	0	2 (0.3)	2 (0.2)
ALT or AST >10×ULN	0	0	0	0

Subjects are counted only once in the highest elevation category. Phase III trials [5,23–25,26].

10 mg group. The first subject was 50 years old with a Body Mass Index (BMI) of 27.9 kg/m² who showed ALT 3.2×ULN and AST 2.9×ULN at week 5 of the three-month course. All ALT values reverted to normal levels at week 9 and remained like this during treatment and up to the 6-month trial follow up. The second subject was 34 years old with a BMI of 18.1 kg/m² who showed ALT 5.1×ULN, AST 2.8×ULN, and GGT 1.5×ULN only at the 3 months follow-up visit. These values returned to normal levels at the 6-month follow up visit. The third subject was 47 years old with a BMI of 19.4 kg/m² with goiter, who also had normal ALT/AST levels during treatment but showed AST 3.3×ULN, ALT 3.8×ULN, and GGT 2.1×ULN at the 3-month follow-up visit. These values returned to normal levels at the 6-month follow up visit.

No subject showed ALT >3×ULN at any visit in the PEARL II (200 subjects), PEARL III extension (131 subjects), and PEARL extension 2 (64 subjects) trials.

One subject showed ALT >3×ULN in the PEARL III trial (209 subjects). This subject, who received UPA 10 mg, was 38 years old with a BMI 30.5, and medical history of Hashimoto's thyroiditis and irritable bowel syndrome. She was treated concomitantly with pantoprazole in the one year prior to starting treatment and presented at screening with normal ALT/AST levels but with elevated GGT values (1.2×ULN) and elevated creatine kinase levels (3.7×ULN) and a mildly decreased prothrombin time of 12.3 s, but INR <1.0 at all visits. At her one month on treatment visit, ALT 5.8×ULN, AST 3.4×ULN, and GGT 3.9×ULN were noted without any increase in total bilirubin or alkaline phosphatase and she continued the treatment. Re-evaluation at one and two weeks later showed a steady decrease of transaminase values while on treatment. GGT levels decreased but stayed above normal during the entire trial, with levels similar to the screening value.

In the PEARL IV trial (451 subjects), 4 subjects were reported to have ALT >3×ULN during the trial. The first subject (UPA 10 mg) of 44 years old had a BMI of 27.6 kg/m². At screening increased GGT (1.8×ULN), progressing at baseline to GGT 2.4×ULN with no significant elevations in ALP. At the 2nd month on treatment, ALT 3.5×ULN with AST 1.9×ULN, ALP 3.0×ULN, and GGT 12.4×ULN were observed. Values decreased subsequently, however the subject withdrew consent to participate further in the trial.

The second subject (UPA 10 mg) of 34 years of age with a BMI of 24.6 kg/m², showed ALT 1.7×ULN at the end of 1st treatment course. One month later (unscheduled visit), values shifted to ALT 3.9×ULN. This subject also withdrew consent and no further values were reported.

A third subject (UPA 10 mg) was 47 years old with a BMI of 26.3 kg/m². The subject showed high ALT at screening and at baseline with values of 4.3×ULN. She was diagnosed with cholelithiasis 10 days later. Despite these values, she was enrolled into the trial. After two months, all liver tests were normal, and a scheduled cholecystectomy was performed. Nevertheless, at the end of 1st treatment course, ALT increased again to 4.0×ULN. Other liver test values showed slight increases in AST, direct bilirubin and GGT. One month later, the subject had emergency surgery due to a small

intestine obstruction and her liver test results were all within normal range up to end of trial, allowing her to complete all 4 treatment courses in the trial.

The last subject treated with UPA 5 mg, showed ALT>3×ULN at screening only.

3.1.2. Aspartate transaminase

Four subjects showed AST values >3×ULN after administration of at least one dose of UPA. It is important to note that while ALT is liver-specific, elevations in AST may also be associated with damage to skeletal or cardiac muscle or in conditions such as myocardial infarction and rhabdomyolysis.

In the PEARL I trial, one subject (UPA 10 mg) showed AST >3×ULN, her changes are already described with the changes in ALT.

In the PEARL II trial, no subject showed AST >3×ULN at any visit.

In the PEARL III trial, two subjects showed AST>3×ULN. The first subject was the patient discussed previously with changes in ALT who had Hashimoto's thyroiditis and irritable bowel syndrome. The second subject was 28 years old with a BMI of 21.5 kg/m². At her 2nd month visit, she showed AST 3.1×ULN with ALT 1.2×ULN indicating a probably muscular origin of the AST elevation. Other liver test results from this visit were within normal range, except creatine kinase (CK) 33.7×ULN. At an unscheduled visit 9 days later, AST, ALT, and CK had returned to normal range.

In the PEARL III extension and PEARL extension 2 trials, no subject showed AST >3×ULN at any visit.

In the PEARL IV trial, one subject showed AST >3×ULN. This subject (UPA 10 mg) was 43 years old with a BMI of 23.7 kg/m². She showed AST 3.4×ULN with ALT of 2.3×ULN at the 3-month follow-up visit, following a laparotomic myomectomy. She had also taken paracetamol 1 g, 4 times daily for two days and ketoprofen 50 mg, 4 times daily for two days, for post-operative pain.

3.1.3. Total bilirubin

In the Phase III clinical trials, 4 subjects presented total bilirubin values >2×ULN after administration of at least one dose of UPA.

In the PEARL I trial, one subject showed total bilirubin >2×ULN. This subject (UPA 10 mg) was 42 years old with a BMI of 22.7 kg/m² and showed total bilirubin 2.4×ULN at the 6-month follow-up visit. The patient had normal ALT/AST levels throughout the trial.

In the PEARL II trial, one subject showed total bilirubin >2×ULN. This subject (UPA 5 mg) was 33 years old with a BMI of 23.2 kg/m², hypothyroidism, and increased bilirubin in the past 3 years and showed increased bilirubin from screening and at the 2nd month on treatment visit 2.2×ULN, which improved during treatment but remained above the upper limit of normal until the end of the study. The patient had normal ALT/AST levels throughout the trial.

In the PEARL III trial, one subject showed total bilirubin >2×ULN. This subject was 37 years old with a BMI of 21.3 kg/m² and a medical history of Gilbert's syndrome. She showed increased total bilirubin levels from 1st month on

treatment (with ALT of 1.0×ULN and AST 1.2×ULN) throughout the trial and low values of alkaline phosphatase. At the end of the first treatment course, her bilirubin was 2.1×ULN. This subject did not continue into the voluntary extension study (PEARL III extension).

In the PEARL III extension and PEARL extension 2 trials, no subject showed total bilirubin >2×ULN at any visit.

In the PEARL IV trial, 2 subjects showed total bilirubin >2×ULN. The first subject (UPA 10 mg) showed bilirubin >2×ULN only at screening (2.2×ULN). The second subject (UPA 10 mg) was 35 years old with a BMI of 20.8 kg/m². She had chronic sinusitis and Gilbert's syndrome and showed bilirubin of 1.4×ULN at screening, which increased to 3.1×ULN between her 1st and 2nd treatment course. These levels remained elevated up to and including the 3-month follow up visit. The patient had normal ALT/AST levels throughout the trial.

3.1.4. Alkaline phosphatase

In the Phase III clinical trials, 2 subjects showed ALP values >2×ULN after administration of at least one dose of UPA. In the PEARL I study, one subject (UPA 5 mg) had ALP >2×ULN. The subject was 32 years old with a BMI 20.5 kg/m² suffering body ache and fever one week prior to baseline and had high values of ALP from screening (2.1×ULN) and continued with >2×ULN values during the study (highest value: 3.1×ULN at week 9). In the PEARL II, PEARL III, PEARL III extension, and PEARL extension 2 studies, no subject showed ALP >2×ULN at any visit in any group. In the PEARL IV study, one subject (UPA 10 mg) had ALP >2×ULN. This subject was 44 years old with a BMI of 27.6 kg/m² and was described previously in the ALT abnormalities section.

Overall, in the Phase I and II clinical trials, no ALT/AST >3×ULN or total bilirubin >2×ULN values were noted. In the Phase III clinical trials, there were a few cases of transient increases of >3×ULN in transaminases with return to normal values without discontinuation of trial drug due to liver issues.

Among 1,053 subjects exposed in Phase III clinical trials to UPA 5 mg or 10 mg, in total 7 subjects (10 mg group) presented ALT >3×ULN, after at least one dose of UPA, resulting in frequency of 0.7% during the monitoring period up to 4 years.

3.2. Liver-related adverse events from phase III trials

In the reviewed Phase III clinical trials apart from the AEs related to laboratory results (liver tests discussed above), the

following liver disorder SMQ events were reported: liver disorder AE in two subjects, hepatocellular injury AE in one subject and haemangioma of the liver AE in one subject. No concern of hepatotoxicity was identified from these 4 AEs in the Phase III trials.

3.2.1. Safety review of ulipristal acetate

The review of Esmya was initiated at the request of European Commission in November 2017, under Article 20 of Regulation (EC) No 726/2004. This review was carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines. The PRAC issued its final recommendations in May 2018. The PRAC's final recommendations were endorsed by the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, and by the European Commission in July 2018.

The review was triggered by four cases of serious liver injury leading to a hepatic transplantation, (including one with fatal outcome due to complications of the transplantation) that were reported since the marketing authorisation of Esmya in 2012. In addition, 8 cases of severe liver injury, associated with the use of the product were reported. The PRAC reviewed all data available at that time from post-marketing settings and from clinical trials. No signal of hepatic toxicity was identified during the review of non-clinical or clinical trials of Esmya inducing hepatic toxicity; however, abnormal values of ALT/AST were an exclusion criterion as per protocols in most clinical trials.

After considering all the evidence, the PRAC concluded that Esmya may have contributed to the development of some cases of serious liver injury and recommended new measures, that were communicated to physicians and patients, to minimize risk of rare but serious liver injury with Esmya for fibroids. Liver monitoring is detailed in Figure 1.

4. Discussion

UPA is an orally active synthetic selective progesterone receptor modulator (SPRM), characterized by a tissue-specific partial progesterone antagonist effect in the target tissues (uterus, cervix, ovaries, hypothalamus). Esmya is a centrally authorized product available as tablets containing 5 mg of UPA. It is

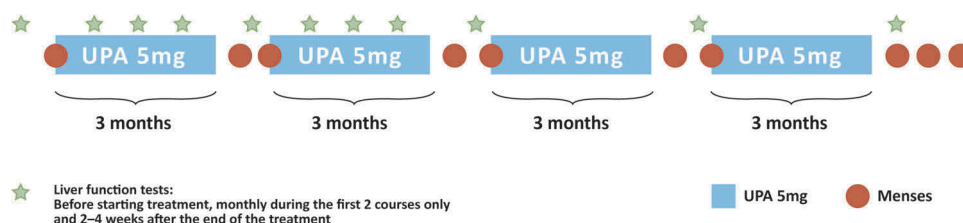


Figure 1. Liver monitoring with ulipristal acetate 5 mg [7]. Liver function tests must be performed before starting treatment. Treatment must not be initiated if transaminases (alanine transaminase (ALT) or aspartate aminotransferase (AST)) exceed 2×ULN (isolated or in combination with bilirubin >2×ULN).

During treatment, liver function tests must be performed monthly during the first 2 treatment courses. For further treatment courses, liver function must be tested once before each new treatment course and when clinically indicated.

If a patient during treatment shows signs or symptoms compatible with liver injury (fatigue, asthenia, nausea, vomiting, right hypochondrial pain, anorexia, and jaundice), treatment should be stopped and the patient should be investigated immediately, and liver function tests performed.

Patients who develop transaminase levels (ALT or AST) >3 times the upper limit of normal during treatment should stop treatment and be closely monitored.

In addition, liver testing should be performed 2–4 weeks after treatment has been stopped (<https://www.ema.europa.eu/medicines/human/referrals/esmya>).

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 was firstly authorized in the European Union on 23 February 2012. The post-marketing exposure to Esmya is estimated to be more than 765,000 patients.

For patients with moderate to severe symptoms due to uterine fibroids who are to undergo surgery, treatment with UPA allows to have rapid relief from heavy bleeding, with associated improvement in quality of life, pain, anemia, and volume of fibroids. The reduction in fibroid and uterine volume may allow for an easier or less invasive surgery and in some cases to avoid it [29].

In patients with moderate to severe symptoms due to uterine fibroids who are not candidates for surgery due to the associated risks and/or potential impact on fertility, or if women do not wish to undergo surgery, intermittent treatment courses with UPA provide the only long-term medical alternative to surgery. The long-term control of fibroid-related uterine bleeding, both during and between treatment courses, the correction of anemia, the reduction of pain, the restoration of a normal QoL, and the significant reduction of fibroid and uterine volume shown to be increased with repeated treatment courses are clinically relevant and important points when considering medical alternatives to surgery. UPA has been developed to treat most of the moderate to severe symptoms caused by uterine fibroids and there is currently no other efficacious medical alternative for long-term treatment of moderate to severe symptoms of uterine fibroids.

During the post-marketing experience with Esmya, sporadic cases of liver injury and hepatic failure were reported. No findings of liver injury were detected in the complete clinical development program of Esmya, with a detailed analysis of individual liver test values presented in this article.

Acute liver injury may be considered as the most common cause for acute liver failure in the USA [30] and Europe [31], with drug-induced liver injury accounting for less than 1% of cases. According to prospective surveys in France and Iceland, DILI occurs with an annual incidence of about 14–19 per 100,000 inhabitants [32,33].

DILI arises from an interplay between pharmacodynamic drug properties acting with specific genetic/non-genetic host factors; reactions which, in idiosyncratic form, are not predictable from drug dosing [34]. The idiosyncratic and diverse disease presentation in DILI makes research challenging as the mechanistic understanding of this condition is still limited. DILI is typically a clinical diagnosis of exclusion and management includes prompt cessation of the offending drug with supportive and symptomatic care [8,9].

By definition, idiosyncratic DILI does not show a clear dose-response relationship [34]. In the case of idiosyncratic hepatotoxicity, the relative importance of host factors determining special individual vulnerability of the affected persons is much more important than the toxic properties of the drug itself [34].

Unfortunately, some individuals exposed to a therapeutic dose may develop idiosyncratic DILI that might involve severe

clinical outcomes, and no biomarker is currently available to identify the susceptible patients prior to drug treatment [35].

UPA is metabolized in the liver by cytochrome P450 3A4 isoform (CYP3A4) [36]. The current product information warns about the co-administration of moderate and potent CYP3A4 inhibitors and UPA is not recommended to avoid increased exposure. Co-administration with CYP3A4 inducers is not relevant in this issue as exposure to ulipristal will then significantly decrease. In vitro studies or pre-clinical data of UPA did not indicate any particular risk for DILI.

A detailed review of the clinical trials carried out in the development of UPA 5 mg was undertaken to further assess the liver data reported during the trials. At the time of this review, the role of UPA as a potential DILI-inducing agent was not clear.

No signal of hepatic toxicity was identified during the review of non-clinical or clinical trials with UPA inducing hepatic toxicity. No elevations of liver enzymes of concern were observed in the phase I and II trials. In phase III trials, the analysis of liver tests showed that in very few patients, there had been isolated and transient increases in some liver enzymes before, during and/or after treatment. However, no findings with respect to UPA raised particular concern. No patients met Hy's Law criteria.

The absence of findings in clinical trials has to be interpreted with caution as abnormal values of ALT/AST were an exclusion criterion as per study protocols. Of note, it should be kept in mind that in the Phase III trials, no patients with pre-existing hepatic disorders or alcohol abusers were enrolled into the trials.

UPA was well-tolerated and there have been no safety concerns related to liver injury with up to eight courses of UPA 10 mg (i.e. twice the marketed dose) followed by off drug intervals allowing the endometrium to shed. Overall, patients did not gain weight, blood pressure was not altered, and biological assessments indicated neither adverse impact on glycaemia or lipids, nor on liver, thyroid, adrenal, and renal functions. Oestradiol levels remained well above menopausal levels avoiding adverse impact on bone mineral density. The most frequently reported AEs were mild to moderate headache and hot flushes [25].

Following the safety review conducted by the EMA, although firm conclusions cannot be drawn that these cases were caused by Esmya, the available data raised serious concerns. Currently, the magnitude and nature (e.g. pattern of hepatotoxicity and possible mechanism of action) of the risks are not well understood. The PRAC has concluded that Esmya may have contributed to the development of some cases of serious liver injury and recommended new measures to minimize risk of rare but serious liver injury with Esmya for fibroids.

5. Expert opinion

UPA does not belong to any of the drug classes commonly considered as drug-induced liver injury agents, nor has any molecular features similar to other drugs in the DILIN network. It is not surprising that during the clinical development of a compound, no signs of liver injury are identified, and it is only during post-marketing exposure, that isolated incidences of liver injury and/or hepatic failure have been described. When reviewing all data

available from the clinical trials data there were no cases in the 5 mg UPA group (approved dose) showing any liver enzymes outside accepted ranges. In phase I and II clinical trials, no concerning issues in relation to Esmya utilization were identified. When assessing phase III trials, the exhaustive review presented here demonstrated only isolated transitory elevations in liver function tests either before, while on treatment, or immediately after, in a limited number of cases. However, none of these findings raised any concerning signal in relationship with UPA.

It is unfortunate that a few subjects treated with UPA at therapeutic doses may develop idiosyncratic DILI; however, susceptible individuals cannot currently be identified by individual biomarkers before treatment.

Due to this, liver toxicity was never suspected based on the data from clinical trials. UPA was well tolerated and no safety signals related to liver injury during clinical development (with up to 8 treatment courses) have been previously identified.

Taking into account that isolated cases of acute liver failure occurred after treating approximately 765,000 patients with no observed signs of liver injury in clinical trials, it is possible to hypothesize that this is a rare idiosyncratic type of DILI. Risks of developing DILI will be minimized by excluding patients with liver function anomalies or hepatic disorders before treatment and by monitoring liver enzymes during treatment. Moving forward, the EMA has recommended periodic liver monitoring before, during, and after treatment with UPA in all patients to be treated, hoping at minimizing the risk of developing liver failure with this therapy and has considered that the benefit-risk ratio of the compound remains favorable if risk minimization measures are followed [7].

Based on the recent EMA review, the benefit/risk ratio of UPA remains positive, considering that currently there is no other long-term medical treatment as an alternative to surgery for the treatment of moderate and severe symptoms of uterine fibroids.

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Declaration of interest

J Donnez has been a member of the Scientific Advisory Board (SAB) of PregLem S.A. since 2007. He held PregLem stocks related to SAB activities that he sold in October 2010 at PregLem's full acquisition by the Gedeon Richter Group. There is no relationship between stock payment value and future commercial performance of the study drug. P Arriagda and M Marciniak are employees of PregLem S.A. D Larrey is a member of the advisory board at PregLem S.A. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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