Therapeutics and Clinical Risk Management

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Hepatic Safety Considerations in the Use of Ulipristal Acetate for Symptomatic Uterine Fibroids

Annika Semmler[1,2,*], Maria E de Lange[2,*], Joost PH Drenth[3], Niels S Vermeer[4], Pierre M Bet[4], Judith AF Huirne[1,2], Wouter JK Hehenkamp[1,2]

[1]Amsterdam Reproduction & Development Research Institute, Amsterdam, the Netherlands; [2]Department of Obstetrics and Gynecology, Amsterdam University Medical Center, location AMC and VUMC, Amsterdam, the Netherlands; [3]Department of Gastroenterology and Hepatology, Amsterdam Gastroenterology Endocrinology Metabolism (AGEM), Amsterdam University Medical Center, Location VUMC, Amsterdam, the Netherlands; [4]Department of Clinical Pharmacology and Pharmacy, Amsterdam University Medical Center, Amsterdam, the Netherlands

*These authors contributed equally to this work

Correspondence: Maria E de Lange, Department of Obstetrics and Gynecology, Amsterdam University Medical Centers, Meibergdreef 9, Amsterdam, 1105 AZ, the Netherlands, Tel +31205667481, Email m.e.delange@amsterdamumc.nl

Introduction: Ulipristal acetate (UPA, 5 mg) demonstrated efficacy in symptom reduction for patients with symptomatic fibroids. While registration and post-marketing trials assessing UPA identified few hepatic concerns, post-marketing concerns about potential drug-induced liver injury (DILI) led to significant restrictions, including indication restriction, warning labels and mandatory liver function monitoring. These measures, along with two marketing suspensions, resulted in a decline in UPA use, ultimately leading to the withdrawal of its marketing authorization previously in Canada, Australia, as well as Singapore and in 2024, at the request of the marketing authorization holder for commercial reasons, also for the European Union.

Methods: This narrative review critically evaluates the hepatic safety considerations associated with UPA.

Results: On reassessment, the risk of severe DILI with UPA is low at 13.5:100.000, with an incidence of 1 in 200,000 for liver transplantation. These numbers are lower than with many other widely prescribed medications, where no regular liver monitoring is recommended. UPA was subjected to strict liver test monitoring although proof of effectiveness of these measures in preventing serious DILI was lacking. While the risk of severe hepatotoxic events is important to consider, a balanced approach to safety measures is needed, particularly in light of the higher risks associated with alternative treatment options such as surgical intervention.

Conclusion: While UPA had a unique place in the treatment of uterine fibroids, overly cautious regulatory measures due to exceedingly rare DILI incidences led to the withdrawal of its marketing authorization in most parts of the world. There is a need for an improved understanding of DILI mechanisms and causality assessments to aid in the development of more proportional regulatory responses, balancing patient safety and sustained access to effective innovative treatment.

Keywords: leiomyoma, drug-induced liver injury, safety pharmacology, selective progesterone receptor modulator, pharmacovigilance, ulipristal

Introduction

Ulipristal acetate (UPA) is a selective progesterone receptor modulator, registered for the treatment of symptomatic uterine fibroids in premenopausal women (Esmya®). Uterine fibroids are benign smooth muscle tumors arising from the myometrium, most common during reproductive age, with a prevalence of up to 70%, and a significant negative influence on quality of life, necessitating surgical interventions in about 25% of women with fibroids.[1] Symptoms include heavy menstrual bleeding, pain, bulk symptoms and reproductive dysfunction.[2]

Registration trials preceding marketing authorization in Europe (2012) and Canada (2013) proved UPA effective in reducing heavy menstrual bleeding and displayed a meaningful and possibly lasting fibroid volume reduction.[3–7] The

Received: 18 July 2024
Accepted: 25 February 2025
Published: 19 March 2025

initial indication for UPA, pre-operative treatment of symptomatic fibroids for up to 3 months, was extended in 2015 to include intermittent treatment (see timeline Figure 1). This extension was based on trial outcomes showing remarkable benefits of intermittent UPA treatment, with 73% of patients achieving control of bleeding after four intermittent 12-week treatment periods. Additionally, there was a clinically significant median reduction in fibroid volume of 71%, which, contrary to post GnRH agonist, was sustained at 65% volume reduction at three months post UPA treatment.[3] Even though treatment with mifepristone, another selective progesterone receptor modulator, had previously shown promising results in terms of bleeding control and some fibroid volume reduction, widespread uptake into clinical practice did not take place.[8,9] For a successful outcome on bleeding control as well as uterine and fibroid volume reduction, existing treatment options were predominantly invasive (embolization, myomectomy, or hysterectomy). Given the high prevalence of fibroids, an increasing preference for uterine-preserving treatment options, and the impressive results of the trials, it is no surprise that the uptake into clinical practice of intermittent UPA treatment increased rapidly. A steep rise in post-marketing prescriptions was seen accumulating to 960,000 in the European Union (EU) up until 2020.[10] One Canadian study reported that 47% of 1500 women with newly diagnosed symptomatic fibroids started with UPA as initial uterine fibroid symptom treatment.[11]

Reviewing the implementation process, we previously commented on the limited representativeness of the study populations, the lack of evaluation of surgical outcomes as well as the lack of comparative trials for intermittent UPA treatment.[13] Neither cost-effectiveness, patient preferences nor fertility or obstetric outcomes were evaluated. At present, real-world data on intermittent treatment with UPA is still scarce, with predominantly small observational retrospective reports. These reports do demonstrate effective control of bleeding, significant improvements in quality of life (QoL), and suggest a potential positive impact on fertility outcomes, with a variable effect on fibroid volume.[14–16] Results of a comparative ongoing randomized controlled trial (RCT), evaluating UPA in comparison to abdominal myomectomy, hysterectomy or embolization, are waited for.[17,18]

Limitations in the comparative evidence for efficacy of UPA are linked to the hepatotoxic concerns which first arose in 2017 and eventually led to withdrawal of the marketing authorization for pre-operative treatment with UPA in 2020. With risk mitigation measures in place, the indication for intermittent UPA treatment of symptomatic fibroids in premenopausal women, where embolization and/or surgery are not suitable or have failed, was retained. The mitigation measures consisted of regular liver enzyme tests (LFTs, total bilirubin), actively informing patients and prescribing physicians on signs and symptoms of hepatotoxicity and the provision of a patient card.[10] The surfacing hepatotoxic concerns of UPA and installed mitigation measures negatively impacted prescription rates.[19] Moreover, the FDA declined marketing approval due to initial safety concerns in the EU.[20] Previously, marketing authorization for UPA was already

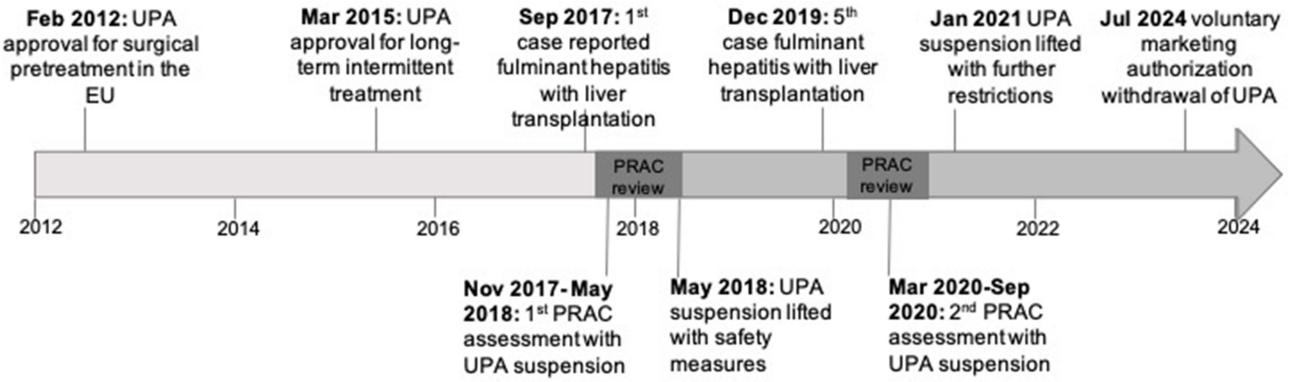

Figure 1 Timeline of UPA marketing authorization and EMA assessment regarding liver failure cases. Reproduced from Middelkoop MA, Bet PM, Drenth JPH, Huirne JAF, Hehenkamp WJK. Risk-efficacy balance of ulipristal acetate compared to surgical alternatives. Br J Clin Pharmacol. 2021 Jul;87(7):2685–2697. http://creativecommons.org/licenses/by-nc-nd/4.0/.[12] May 2018 Risk minimization measurements: contraindication in women with known liver problems; liver tests before, during and after stopping treatment; patient card informing about the need for liver monitoring and to contact their doctor should they develop symptoms of liver injury. Additionally, use for more than one treatment course has been restricted to women who are not eligible for surgery. Jan 2021 Further risk minimization measurement: restriction of UPA use to intermittent treatment of symptomatic uterine fibroids in premenopausal women, when uterine fibroid embolization and/or surgical treatment options are not suitable or have failed. Pre-surgical treatment indication withdrawn. Jul 2024 Withdrawal of marketing authorization for commercial reasons at the request of authorization holder.

withdrawn in Canada (2019) as well as in Australia and Singapore (2020). Eventually, for commercial reasons, the marketing authorization holder has withdrawn UPA also from the European market in July 2024.[21]

While the risk of severe hepatotoxic events is important to consider, a balanced approach to safety measures is needed, particularly in light of the higher risks associated with alternative treatment options such as surgical intervention.[12] Through a search in PubMed, using ulipristal acetate, fibroids, myoma and leiomyoma as search terms, we identified randomized controlled trials, prospective and retrospective cohort studies, reporting on efficacy as well as hepatotoxicity. In this manuscript, we critically assess the current data on UPA hepatotoxicity and identify knowledge gaps and lessons learned that could help improve a more balanced regulatory approach ensuring both patient safety and continued access to effective treatments.

How Was UPA Associated With Drug Induced Liver Injury?

Throughout the registration trials, no safety concerns arose related to drug-induced liver injury (DILI) nor were there reported adverse events that met Hy's Law criteria.[22] This is a common biochemical criterion used, also by regulatory bodies such as the European Medicines Agency (EMA). It signals the risk for acute liver failure on the basis of serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin. It is met when the following conditions apply (1) ALT/AST > 3 x upper limit of normal (ULN) (2) total bilirubin > 2 x ULN (3) absence of ALP and (4) the absence of other reasonable explanations resulting in increased ALT and total bilirubin.[23]

Overall, in Phase 2 and 3 clinical trials, over 1,000 participants received at least one course of UPA, and 660 received two or more courses. Throughout these trials, transient elevations in ALT of more than 3 x ULN were recorded in 8 participants with or without the same degree of AST elevations. Four remained on treatment exhibiting a normalization of ALT/AST, one participant had elevations at baseline which normalized upon treatment initiation, and one participant withdrew study consent. In two participants, the ALT elevations were detected 1–3 months post-treatment and normalized thereafter. These LFT elevations did not raise concerns of possible liver toxicity or meet Hy's Law criteria.[22] DILI was, however, considered at the time of marketing authorization, presumably due to findings from preclinical toxicity studies that were compatible with hepatoxicity (increase in liver weight and hepatocellular hypertrophy). The latter data were later judged as nonrelevant to humans. No routine risk minimization measures were implemented, and it was agreed with EMA to further study DILI post-marketing as an adverse event of special interest in the ongoing and planned clinical studies.[24,25]

The first clinical concerns about possible DILI emerged after UPAs marketing authorization. Due to several serious liver injury cases, including five necessitating a liver transplantation, a Pharmacovigilance Risk Assessment Committee (PRAC) review was triggered twice, in 2018 and 2020, suspending UPAs marketing authorization and formally assessing a link between UPA and DILI. Reports of liver injury were assessed, with 33 reports of serious liver injury prior to 2018, and 97 the following two years until 2020.[10,26] Only a small number, however, contained (partially) sufficient information for causality assessment, 16 and 7 cases, respectively. In the initial 2018 report, the PRAC deemed UPA to have a possible role in DILI in 8 cases, 4 of which needed a liver transplantation, 1 of which was fatal due to postoperative septic complications. At this time, no definitive link could be made due to the presence of confounding medication, underlying comorbidities or missing information (cases outlined in Table 1).[26]

As suspension of UPA approval was lifted in 2018, the Risk Management Plan (RMP) was updated, aimed at mitigating hepatotoxic risks. These included a contraindication for patients with underlying liver disease, introducing a patient card to ensure the patients' awareness of the risks, and a risk communication to prescribing physicians recommending regular LFTs before the start and throughout the treatment courses. A second PRAC review was triggered in 2020 by a 5th case of liver failure leading to liver transplantation that occurred in spite of adherence to the risk minimization measures. For this case, it was concluded that there was sufficient evidence to establish a probable/highly probable link to UPA. While normal LFTs were measured before the start of UPA, elevated transaminases (>5 x ULN after 58 days of treatment) were treatment emergent and the clinical picture deteriorated into liver failure in spite of treatment cessation. DILI-related symptoms started 6 weeks after treatment termination and the patient received a liver transplantation 2 weeks thereafter. For this patient medications and underlying comorbidities that could provide alternative diagnoses or etiologies were ruled out, and the likelihood that the DILI was a result of UPA was deemed to have a "considerably higher degree of certainty".[30,31] Four other cases were thought to have a possible link to UPA

https://doi.org/10.2147/TCRM.S273358

Table 1 Post-Marketing Liver Injury Reports Prior to 2018

Serious Liver Injury Case	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Cases of liver transplantation	**1**	**2**	**3**	**4**	n/a	n/a	n/a	n/a
Time of incident	2014	2017	2017	2018	<2018	<2018	<2018	<2018
Age (years)	55	58	45	46	54	48	38	48
Reason for UPA discontinuation	Treatment completion (109 days)	Symptoms	Symptoms	Treatment completion (6 months continuously?)	Increased LFT	Symptoms	–	Symptoms
Symptom onset	2 days into 1st course	2 months into 1st course	3 days into the 1st course	16–20 days after discontinuation	–	10th day of 2nd course	2.5 months into 1st course	–
Initial reported symptoms reported	Fatigue, asthenia, anorexia, post-prandial fullness	Fatigue, nausea	Asthenia, nausea, vomiting, dark urine	Appetite loss, nausea, jaundice, rash	Decreased appetite, fatigue, jaundice, dark urine, weight loss	Nausea, abdominal pain, fatigue, jaundice	Jaundice	Abdominal pain, nausea, fatigue
First increased LFTs (AST/ALT in IU/L)	3 days after completion of 1st course (1443/1920)	1 week after discontinuation (1592/2206)	26 days into 1st course (1611/1322)	At onset of symptoms (1194/1008)	3.5–4.5 months after 1st dose (1039/1916)	Concomitant with symptoms	2.5 months into 1st course (3962/5558)	2 months into 2nd course (2500s)
Time to liver transplantation	6 weeks after last dose	4 weeks after last dose	4 weeks after last dose	5 weeks after last dose (Fatal)	n/a	n/a	n/a	n/a
Last normal LFT	6 months before UPA	3 years before UPA	-	Before UPA treatment	-	-	-	-
Regular LFT tests	-	-	-	-	-	-	-	-
Missing information	yes	no	yes	yes	yes	yes	yes	yes
Confounding medication	yes	no	no	no	yes	-	yes	-
Confounding condition	no	yes	no	yes	yes	yes	yes	yes
Causality assessment	possible	possible	probable	possible/probable	possible	possible	possible	possible

Notes: Liver injury cases collected for the PRAC assessment in 2018. 33 cases of serious liver injury reports of which 17 had (partially) sufficient information for causality assessment. Displayed are the serious liver injury cases where UPA was deemed to have a possible role. n/a = not applicable. Information derived from official documents of the EMA concerning the PRAC assessment report and scientific conclusion,[10,26] Kang et al[27] Dini et al[28] Meneur et al[29].

(Table 2). The PRAC recommended revoking the marketing authorization of UPA. The Committee for Medicinal Products for Human Use (CHMP) opposed the PRAC's overall conclusions and grounds for recommendation and determined that the benefit-risk balance of UPA for symptomatic fibroids remained favorable. Changes to the terms of the marketing authorization were recommended to restrict intermittent UPA use to women with symptomatic fibroids when embolization and/or surgical treatment options are not suitable or have failed, while revoking the pre-operative treatment indication.[30]

Hepatic Outcomes in Clinical Studies Since Marketing Authorization

Since marketing authorization, various studies have been published assessing UPAs effectiveness and safety. While the majority of the studies were conducted before the initial report in 2018 was released, most findings were published thereafter. Studies reporting on safety aspects during these trials are outlined in Table 3 and Table 4.

Table 2 Post-Marketing Liver Injury Reports Between 2018–2020

Serious Liver Injury Case	**1**	**2**	**3**	**4**	**5**
Cases of liver transplantation	1	n/a	n/a	n/a	n/a
Time of incident	2019	<2018	>2018	>2018	>2018
Age (years)	58	48—49	45	52	34
Reason for UPA discontinuation	Increased ALT/AST	symptoms	Increased LFT	–	–
Symptom onset	6 weeks after discontinuation	81–82 days of 1st course	–	–	–
Initial reported symptoms reported	Nausea, vomiting, jaundice	Nausea, right upper quadrant abdominal pain	–	–	–
First increased LFTs (AST/ALT in IU/L)	58 days after initial dose (182/321)	Presumably after 1st course	Presumably in 6th treatment course	Unknown timing, during or after course	4th course
Time to liver transplantation	8 weeks after last dose	n/a	n/a	n/a	n/a
Last normal LFT	Before UPA treatment	–	–	–	–
Regular LFT tests	yes	no	yes	yes	yes
Missing information	no	yes	yes	yes	yes
Confounding medication	no *	yes	yes	yes	yes
Confounding condition	no	–	yes	–	–
Causality assessment	Probable/highly probable	possible	possible	possible	possible

Notes: Liver injury cases collected for the PRAC review in 2020. 97 cases of serious liver injury reports of which 7 had (partially) sufficient information for causality assessment. Displayed are the serious liver injury cases where UPA was deemed to have at least a possible role. Regular LFT testing and normal LFT prior to UPA start is assumed, however not mentioned in the EMA report. n/a = not applicable. * see discussion section. Information derived from official documents of the EMA concerning the PRAC assessment report and scientific conclusion[10,26] Carballo et al[28].

https://doi.org/10.2147/TCRM.S273358

Table 3 Phase II–III Clinical Trials Outside EU Assessing UPA

Trial	Objective	Country, Year	UPA Dosage mg (+ Comparator)	Duration Treatment (days)	No. per Group	Increased ALT or AST > 3x ULN	Transient	SAE of UPA Related Hepatotoxicity
Irahara et al, 2020[32]	Efficacy and safety, dose finding	Japan, –	2.5 5 10 leuprorelin placebo	84	24 24 25 24 24	no	-	no
Westhoff et al, 2021[33]	Evaluation of ovulation and safety	US 2014–2016	5 10 5 + placebo	84 24	61 59 60	1 (>2 x ULN)	-	no
VENUS I[34]	Efficacy and tolerability	US 2014–2016	5 10 placebo	84	53 48 56	no	-	no
VENUS II[35]	Efficacy and tolerability	US 2014–2016	5 10 placebo	84 (1: 2 courses)	162: 84 157: 82	no	-	no
Osuga et al, 2021[36]	Efficacy and safety of long-term intermittent treatment	Japan, 2017–2019	10	84	140	no (2: < 3 x ULN)	upon treatment discontinuation	2 (however ALT/AST < 3 x ULN)
Osuga et al, 2021[37]	Non-inferiority trial	Japan 2017–2019	10 leuprorelin	84	82 80	no (3: < 3 x ULN)	yes; treatment discontinuation of 2	no
Summary				84	1,001	no (6 < 3 x ULN)	yes	2 (however ALT/AST < 3 x ULN)

Clinical Phase II-III Trials Outside EU

A number of clinical trials have been conducted in countries outside of the EU to assess UPAs safety and efficacy in other populations with often similar exclusion criteria and regular LFT testing comparable to the initial registration trials. A total of 1,001 participants have had at least one course of 5 to 10 mg UPA daily in clinical phase II–III trials regularly assessing liver tests. In Japan, a trial assessing the efficacy and safety of UPA, and a non-inferiority trial comparing it to leuprorelin enrolled a total of 222 participants receiving 10 mg UPA for one course.[36,37] Three participants had transient ALT/AST increases below 3 x ULN, with two discontinuing treatment at the discretion of the investigator. Elevated liver enzyme levels were also reported in one leuprorelin recipient. Eight participants had hepatic AEs related to UPA treatment, with two severe cases leading to discontinuation but with AST/ALT still below 3 x ULN, thus not meeting Hy's law criteria. Mean ALT/AST remained stable throughout treatment. Westhoff et al[33] also reported on one participant with elevated ALT/AST above 2 x ULN. The UPA dosage and degree of ALT/AST elevation is unknown. Throughout the VENUS I–II trials 586 participants received either 5 or 10 mg UPA for at least one course. Neither hepatic injury related to UPA, nor abnormal liver transaminases were reported.[34,35,49]

Real-World Data

A prospective non-interventional study called PREMYA was conducted in 2012 to 2014, where 1,473 patients received 5 mg UPA as preoperative treatment for up to 3 months.[38] There were no hepatotoxic related (S)AEs reported in this study, LFTs, however, were not measured. Several other cohort studies were conducted prior to the risk minimization efforts in 2018 in Italy,[41] Belgium,[40] Korea,[14,50] Portugal,[42] and Spain[39] with a total of 1,430 participants being treated with at least 1 course. None reported hepatotoxic related SAEs; however, standard liver transaminase testing was not

Table 4 Real-World Post-Marketing Trials Assessing UPA

Trial	Objective	Country, Year	UPA Dosage mg (+ Comparator)	Duration Treatment (days)	No. per Group	Increased ALT or AST > 3x ULN	Transient	SAE of UPA Related Hepatotoxicity
Study conducted before 2018								
PREMYA 2017[38]	Prospective cohort study of 'real-world data'	European Union 2012–2014	5	84	1,473	-	-	no
Gracia et al, 2018[39]	Retrospective cohort study to assess UPA effect on concomitant adenomyosis	Spain, 2015–2016	5	84	153	-	-	no
Verguts et al, 2019[40]	Prospective cohort to assess if UPA can reduce invasive surgery	Belgium, 2014–2016	5	84	222	-	-	no
Hong et al, 2019[32]	Retrospective cohort to assess adverse symptoms	Korea, 2016–2017	5	16–84	100	no (of 14 women)	-	no
Giarre et al, 2020[41]	Retrospective cohort study on effectiveness and safety	Italy, 2014–2017	5	1–4 courses	142	-	-	no
Aguas et al, 2020[42]	Retrospective cohort study	Portugal, 2017	5	1+ course	526	-	-	no
MYOMEX 2020[43]	Non-inferiority RCT	Netherlands, 2015–2017	5 Leuprorelin	84	29 25	-	-	no
Yoon et al, 2021[44]	Nationwide retrospective cohort study to assess liver disease	South Korea, 2010–2018	5 GnRHa	-	11,445 (UPA) 11,445 (GnRHa)	-	-	Total liver disease (RR 1.11) Mild liver disease (RR 1.09) Severe and toxic liver disease did not differ
Study conducted around or after 2018								
Neri et al, 2019[45]	Observational study for bone turnover and quality of life	Italy,-	5	2 courses	22	no	-	no
Del Forno et al,2020[46]	Cross-sectional study to evaluate liver function	Italy, 2018	5	At least 1 course	162	no	-	no
Morgante et al, 2020[15]	Prospective cohort study to assess fertility	Italy, 2017–2018	5	1–3 courses	27	no	-	no
Jha et al, 2021[47]	Prospective efficacy and safety study of long-term UPA	India, 2020–2021	5	2 courses	94	no	-	no
UCON 2023[48]	Safety and tolerability and effectiveness of UPA vs levonorgestrel IUD	United Kingdom, 2015–2018	5 Levonorgestrel IUD	3 courses of 84	118 118	3 (of 55 measurements)	upon treatment discontinuation	1 (acute hepatitis)
Kyeong et al, 2023[14]	Efficacy of long-term UPA in retrospective cohort	Korea, 2016–2019	5	1 course 4 courses	168 119	-	-	no
Summary				At least 1 course	3,355 *(excl. Yoon* et al *2021)*	3 (of 661)	Yes	1

Notes: Studies conducted after 2018 will likely have followed the risk minimization strategies implemented by the EMA with regular LFT testing. Only Kyeong et al 2023 does not report on LFTs.

https://doi.org/10.2147/TCRM.S273358

performed in any of these cohorts. As a response to the first risk minimization effort of the EMA in 2018, Del Forno et al conducted a cross-sectional study, notifying participants of the EMA investigation on UPA related DILIs, and inquiring about side-effects as well as testing liver transaminases. Among 162 participants with a mean UPA treatment duration of 1.8 courses, there were no increases of ALT/AST and no symptoms indicative of liver injury.[46]

Only a few studies were conducted after or during the implementation of the risk minimization strategies of 2018 and had therefore regular liver assessments throughout the trials. The majority of these were small in number and observational in nature.[15,45,47] None reported abnormal LFTs. The most recent publication of a study conducted in 2016–2018, comparing levonorgestrel intra uterine device (IUD) to UPA 5 mg in the United Kingdom, reported that 3 of 55 participants who underwent regular liver tests, had ALT/AST elevations of more than 3 x ULN, 2 during treatment and 1 post-treatment. None of these participants required hospitalization and transaminase levels normalized upon discontinuation. No further information was provided as to whether UPA was deemed the cause or if further analyses were done to rule out other causative agents. Additionally, the study reported one participant on her last course of UPA developing acute hepatitis requiring steroid treatment. The authors, however, note that this patient had a strong family history of autoimmune hepatitis and would have likely been excluded with the newly implemented liver function eligibility test.[48]

Moreover, Yoon et al[44] conducted a nationwide retrospective cohort study in South Korea using the Health Insurance Review and Assessment Service data. The aim was to assess incidences of reported liver disease in patients treated with 5 mg daily UPA as compared to gonadotropin releasing hormone agonist (GnRHa) such as leuprorelin. After a 1:1 propensity score matching, 11,445 participants per group, treated between 2013 and 2018, were assessed. When assessing severe liver disease, hepatic failure, or toxic liver disease reporting, no statistically significant differences were found between the UPA group and GnRHa group. Only total liver disease (RR 1.111, 95% CI 1.015–1.216), mild liver disease (RR 1.094, 95% CI 1.000–1.196) and "other diseases of the liver" (RR 1.106, 95% CI 1.007–1.214) were found to be higher amongst patients treated with UPA, compared to GnRHa. In addition, the authors reported a severe liver disease incidence of 0.04% among patients treated with UPA and 0.03% among patients treated with GnRHa. No liver transplantations were recorded. As this was a review using a health insurance database, no information is available on LFTs in the exposed population.

What Is the Incidence of UPA Associated DILI?

From the initial marketing authorization in 2012 to 2018, approximately 765,000 patients had been exposed to UPA 5 mg in the EU.[10] The liver transplantation reporting rate for this period was equivalent to 0.52:100,000 UPA users. In the time between the initial PRAC review in 2018 and the review conducted in 2020, an additional 194,614 patients were exposed to UPA and 1 liver transplantation was reported. The reporting rate of liver transplantation with UPA use therefore remained around 0.52:100,000.[30] To evaluate liver injury reporting among UPA users, the EMA used Standard Sets of MeDRA Queries (SMQ) of the hepatic disorder spectrum. Serious liver disorder SMQs increased between 2018 and 2020, with 33 reports during the first PRAC review in 2018, and 97 reports the following two years, likely due to the community's vigilance to report liver-associated diseases of patients on UPA treatment. However, only 16 and 7 of these reports, respectively, had enough information for causality assessment making it difficult to assess the true DILI incidence. Postulating all serious liver injury cases reviewed by the PRAC as "possible" were in fact true UPA-related DILIs, the overall serious DILI incidence would be equivalent to 1.35:100,000, based on 15 cases and the above-mentioned exposure. This incidence could potentially be higher considering a large number of cases were not assessable, leading to a conservative calculation of 13.5:100,000 based on 130 serious liver disorder SMQs. Of note, these likely also include reports of non-drug related hepatic disorders, and cases where sufficient evidence was present yet the EMA deemed an UPA related DILI unlikely. This incidence is still in line with the estimated incidence of DILI in the general population. In France, a population-based study revealed an annual incidence of 13.9 cases per 100,000 inhabitants.[51] Similarly, Iceland and Korea reported incidence of 19 and 12 per 100,000 inhabitants respectively.[52,53]

Since 2020, no further serious liver injury cases have been reported by EudraVigilance,[54] nor found through a literature search. However, UPA treatment numbers also drastically declined. Quantitative analysis of LFTs to assess hepatotoxicity is difficult to assess due to lack of data, as prior to 2018, testing was not done routinely, nor was this a common outcome measure in early post marketing studies reporting on UPA. In the initial PRAC review of 2018, the

PRAC recommended a retrospective cohort study to be conducted using EU national databases to assess the absolute and relative risk of liver injury with UPA use.[26] This study, however, was canceled due to insufficient UPA exposure.[55] Furthermore, for several large post marketing trials mentioned in the EMA report, no data has yet been published.[56–58] As previously mentioned, the largest cohort evaluating severe/toxic liver disease used an insurance database, for claims for UPA as well as fibroid diagnosis (Yoon et al).[44] No increased incidences of severe liver disease, hepatic failure or toxic liver disease were seen in UPA users compared to GnRHa users, individual LFT analyses, however, were not available. Underreporting of liver toxicity is a possibility.

Can We Predict DILI Risk With UPA?

While DILI is a leading cause for withdrawal of a drug during Phase I, II and III trials, and hepatotoxicity is the most common reason for post marketing withdrawal, predicting accurate odds of hepatotoxicity has proven to be very challenging.[59] DILI is a poorly understood adverse drug reaction, which can be elicited by nearly all classes of medication. DILI can be classified into either intrinsic, which is more predictable and dose-dependent, or idiosyncratic, which has an unpredictable nature.[60] As evidenced by the cases assessed by the EMA (see Table 1 and Table 2), the liver injuries reported as possibly associated with UPA were highly heterogenous. Women affected had a broad age range, have had varied exposure time before the onset of symptoms, and for some patients, symptoms only appeared after treatment cessation. The mechanisms of a UPA-related DILI remain unclear and are believed to be of an idiosyncratic nature and therefore unpredictable Factors like concomitant disease, age, sex, genetic factors and compound-specific factors may have a contributing role; however, studies looking into risk factors for DILI have not been conclusive.[60] A published case report of one of the five patients that had a liver transplantation postulated a possible association between the reactivation of human herpes virus-6 and the degree of adverse drug reaction.[61] There appears to be a genetic predisposition to DILI, as in the case of HLA loci polymorphism and amoxicillin/clavulanate induced DILI,[62] and flucloxacillin-induced hepatotoxicity.[63] However, the diagnostic value of genetic testing is still limited due to a low positive predictive value for screening before drug usage, and has not been assessed with UPA.[64]

How Effective are the Current Risk Minimization Strategies?

While hepatotoxicity and DILI are common concerns with pharmaceutical treatments, many Risk Evaluation and Mitigation Strategies (REMSs - FDA), specifically, those with Elements to Assure Safe Use (ETASU), or risk minimization measures (RMMs - EMA) are put in place to increase drug safety. These often involve complex processes and elaborate measures, with significant impact for patients as well as prescribers. In general, data providing evidence on the effectiveness of REMSs or RMMs, however, is lacking.[65] Since the implementation of additional RMMs for UPA in 2018 and until the PRAC review in 2020, an increase in serious liver injury SMQ reports was seen. Only a small proportion of reports contained enough information for causality assessment. Importantly, the 5th liver transplantation case developed liver failure after exposure to UPA despite adherence to risk minimization measures with regular LFTs and timely treatment secession upon LFT elevations. Current risk minimization strategies might therefore not be effective in preventing progression into liver failure for all patients, a consideration also noted by the PRAC in 2020.[10,30]

How Do Other Drugs With DILI Risk Compare?

Various methods and datasets have been used to identify a multitude of drugs linked to DILI. Idiosyncratic DILI is a highly challenging disease to diagnose, with varying definitions, reporting issues, and low incidences. Several studies have implicated amoxicillin-clavulanate as the most frequent drug linked to DILI (beside acetaminophen use).[66,67] Other agents frequently reported to cause DILI include commonly used drugs like diclofenac and nitrofurantoin. Björnsson et al[52] conducted a prospective population-based study in Iceland, to investigate the incidence and clinical characteristics of DILI. In this study, amoxicillin-clavulanate as well as nitrofurantoin and diclofenac were implicated as common agents linked to DILI. The study further estimated the risk of drug-associated DILI based on the DILI incidence and the number of outpatient patients taking the drug (see Table 5).

When comparing these incidences to our abovementioned UPA-associated DILI risk calculation, antibiotics such as nitrofurantoin and amoxicillin-clavulanate, although commonly used short-term, had a higher risk of DILI than UPA would

Table 5 DILI Incidence for Different Drugs and Associated Risk Minimization Methods

Medication	Likelihood Score	LFT Advice on SMPCs
Azathioprine	A	Routine LFTs during treatment[68]
Infliximab	A	Regular LFT during treatment[69]
Isotretinoin	D	LFTs before start, 1 month after treatment and at 3 monthly intervals[70]
Nitrofurantoin	A	*With prolonged use and/or signs of hepatitis hepatic function monitoring is advised*[71]
Amoxicillin-clavulanate	A	*With prolonged use hepatic function assessment is advised*[72]
Atorvastatin	A	LFTs before start and periodically during treatment[73]
Diclofenac	A	*With prolonged use hepatic function monitoring is advised*[74]
Ulipristal acetate	C	LFT before treatment, monthly in the first 9 months, then before and after a treatment course, patient warning card given[75]

Notes: Likelihood scores[76] were derived from LiverTox with the exception of UPA. Category A : drug is well known, well described and well reported to cause either direct or idiosyncratic liver injury, and has a characteristic signature; more than 50 cases including case series have been described.Category B: drug is reported and known or highly likely to cause idiosyncratic liver injury and has a characteristic signature; between 12 and 50 cases including small case series have been described.Category C: drug is probably linked to idiosyncratic liver injury, but has been reported uncommonly and no characteristic signature has been identified; the number of identified cases is less than 12 without significant case series.Category D: single case reports have appeared implicating the drug, but fewer than 3 cases have been reported in the literature, no characteristic signature has been identified, and the case reports may not have been very convincing. Thus, the agent can only be said to be a possible hepatotoxin and only a rare cause of liver injury.

Abbreviation: SMPC = summary of product characteristics; DILI = Drug induced liver injury; LFT = liver function tests.

(73:100,000, 95% CI 20–187; 43:100,000, 95% CI 24–70 respectively) (Figure 2). Diclofenac, a commonly used pain medication, had a risk of DILI comparable to that of UPA (11:100,000, 95% CI 4–24). Moreover, a prospective randomized trial found that the incidence of liver-related hospitalization potentially caused by diclofenac use was 23 per 100,000, and the occurrence of Hy's law was 12 per 100,000 patients.[76] The DILI Network likelihood score shown in Table 5 depicts the number

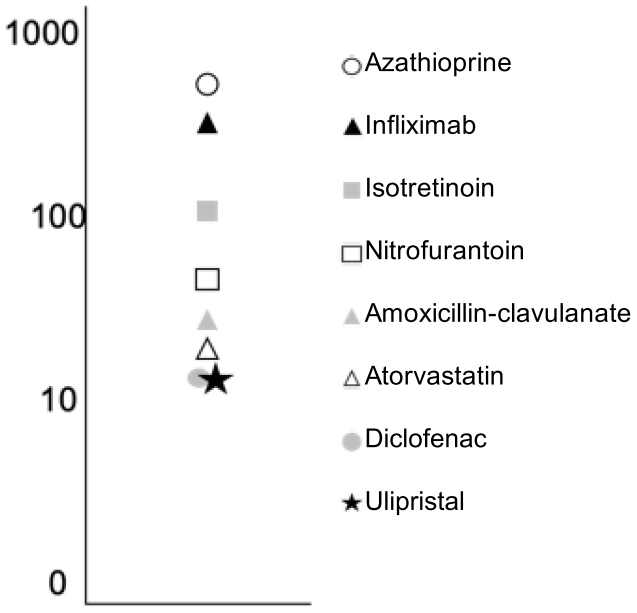

Figure 2 Dili incidence per 100,000 patients. Reproduced from Middelkoop MA, Bet PM, Drenth JPH, Huirne JAF, Hehenkamp WJK. Risk-efficacy balance of ulipristal acetate compared to surgical alternatives. Br J Clin Pharmacol. 2021 Jul;87(7):2685–2697. http://creativecommons.org/licenses/by-nc-nd/4.0/ [12,12] DILI incidence per 100,000 patients is based on the study by Björnsson et al,[52] DILI incidence for UPA is based on a conservative calculation of 130 serious liver disorder SMQ reports and 959,614 prescriptions.[10]

of cases reported in the literature that support the drug as a cause of DILI, not considering the number of prescriptions. Category A represents a well-known link to the drug with more than 50 cases published, while category C indicates a probable link to the drug, with less than 12 cases published.[77] With the limited number of published cases on UPA-related DILI, UPA would fall into category C. Notably, of the agents listed in Table 5, UPA is subject to the most frequent liver function tests and indication restriction, despite the estimated low incidence of UPA-induced DILI and the low likelihood score.

Discussion

Ulipristal was a unique treatment for pre-menopausal women with symptomatic fibroids. It demonstrated significant efficacy in reducing heavy menstrual bleeding and offered a substantial likelihood of alleviating symptoms related to fibroid volume, such as pain, miction problems and potentially subfertility, by reducing the fibroid volume. The latter likely with a long-lasting effect, contrary to any drug previously registered to improve fibroid related symptoms. Especially, when fertility preservation is a priority, it could have offered a beneficial alternative to other more invasive volume reducing treatments, such as surgical removal of fibroids, hysterectomy or embolization. Evidence on this latter claim, however, is lacking. With concerns of hepatotoxicity related to UPA, clinical experience and data collection proved to be difficult. Inclusion rates for the only ongoing RCT assessing the need for secondary intervention after UPA and comparing treatment efficacy were slow,[18] partially because prescribers as well as patients had become apprehensive on initiating UPA for symptomatic fibroids due to concerns over its potential hepatotoxicity and the burden of frequent blood tests. This decline was evident as treatment initiation significantly plummeted. UPA prescriptions in England dropped from 8,940 annually in 2017 to just 16 in 2023, while in the Netherlands, they decreased from 2,585 annually in 2017 to 94 in 2024.[12,78,79] Consequently, marketing authorization for UPA with the European Medicines Agency has been withdrawn upon request of the marketing authorization holder, Gedeon Richter PIc, which notified the European Commission of its decision to permanently discontinue the marketing of the product for commercial reasons.[21] A rare yet serious adverse event, with uncertain causality, has significantly impacted the availability of a potentially promising fibroid treatment.

DILI Reporting and Causality Assessment

To date there is a general lack of understanding of idiosyncratic DILI mechanisms. Current DILI causality assessments strongly rely on a diagnosis by exclusion and expert evaluations which, coupled with abundant missing patient information, can result in an overly conservative conclusion. This approach, while being protective for patients, can also lead to excessively cautious regulatory actions and in the end, the discontinuation of promising therapies. Given the vital role of clinical decision making, diagnostics that better differentiate a DILI from other underlying hepatic etiologies or DILI from concomitant medications are needed to improve causality assessment.[80] We therefore encourage authorities and pharmaceutical industries to embrace new techniques, such as the recently developed in vitro test on blood monocyte-derived hepatocyte-like cells,[81,82] which may better discern the contribution of concomitant medications or supplements. In addition, HLA genotyping, although with a very low positive predictive value for DILI, has a high negative predictive value, and could therefore, where available, rule out drug-induced hepatotoxicity when suspected or even discern the causal agent in polypharmacy.[83]

In addition, spontaneous reports of suspected adverse reactions remain the cornerstone of pharmacovigilance and are particularly essential in the detection of rare and severe adverse reactions. However, current practices regarding the identification of hepatotoxic agents are less reliable than previously believed, as indicated by a pharmaco-epidemiological study using a large database of electronic health records. They found that categorizing the hepatotoxicity based on case reports does not reflect the severity of liver injury rates.[84] With the increasing use of electronic health records, a promising tool with the use of real-world clinical data could supplement case reports to characterize drug-related toxicity and more closely reflect real-world incidences.

Proportional Risk Mitigation

The risk of UPA-related serious DILI appears to be exceedingly low. Nonetheless, in contrast to many other drugs with higher DILI incidences, UPA was subject to stringent indication restriction, liver monitoring and patient warnings

resulting in prescribers and patients being apprehensive of its use. Considering the rising healthcare costs and the low patient compliance with high burden of frequent liver testing, the effectiveness of such rigorous risk minimization measures in detecting rare cases of serious DILI is questionable and may even be counterproductive.[84] While DILI events are very rare, implementation of stringent risk minimization strategies, can result in a significant reduction in newly initiated treatments and a decrease of inclusion rates of subsequent studies aimed at identifying potential risk factors and collecting comparative evidence on efficacy. After the initial PRAC assessment, the manufacturer was asked to conduct several studies to assess the absolute and relative risk of DILI with UPA usage, to identify potential biomarkers in EU registries in the risk of developing DILI after UPA, and to assess possible HLA risk factors for developing severe DILI after UPA.[26] All of these trials had been, however, canceled due to lack of power as a result of a strong decline in demand for UPA treatment.[55]

Risk Communication

In one study, 75% of all patients using UPA at the time of the first marketing revocation declared they would choose UPA again, even after being informed of the newly identified risk of DILI.[46] The patient representative consulted by the CMHP at the second review also agreed that counselling of patients should be the center of decision-making, stressing the importance of choice and informed decision of the individuals taking into account all available options.[30] Effective risk communication and patient counselling are crucial for adequately informing patients about UPA treatment. However, it is equally important to provide clear communication regarding the risks associated with alternative treatments. Our research group conducted a risk-efficacy balance analysis comparing UPA with surgical options such as myomectomy and hysterectomy. The analyses highlight that surgical treatments may carry even higher mortality and morbidity (>1:1,000) compared to the very low risk of UPA-related DILI, conservatively estimated at 0.135:1.000.[12] These risks should be carefully considered and weighed alongside other factors when evaluating treatment options.

In addition, several of the UPA-related DILI cases highlight the importance of awareness of prescribers and communication to patients of possible supplements and medication that have interactions with CYP3A4 metabolizers.[85] In one liver transplantation case linked to UPA, the patient used raspberry leaf supplements, known for menstrual symptom relief and as a CYP3A4 inhibitor, potentially affecting UPA metabolism.[86] In another case, the PRAC considered concomitant use of flutrimazole not a confounding factor for the development of DILI. However, flutrimazole is a miconazole analogue, which in turn is a strong CYP3A4 inhibitor. Although it was dermally used, systemic effects and thus systemic exposure of UPA cannot be ruled out. Grapefruit juice is another well-known potent CYP3A4 inhibitor, which should be actively communicated to patients.[87]

Importance of Comparative Research

Furthermore, an appraisal of clinical guidelines on fibroids confirms a general lack of evidence for almost all treatment strategies, with a lack of comparative trials and primary outcomes that are often not clinically relevant.[88] Early involvement of patients during the post-marketing evaluation process is vital for identifying patients' needs and determining relevant clinical outcome measures. Post marketing, Phase 4, trials are also of vital importance to identify patient subgroups who benefit most from a new treatment, alongside evaluating the longer-term safety profile. Understandably, incentive from the pharmaceutical industry to conduct such trials is lacking, and the route to a robust clinical trial, even more a randomized controlled trial, is long, bureaucratic and requires substantial funding. This results in not only a delay of important additional safety information becoming available but also a missed opportunity in identifying the patient subgroup that most benefit from the treatment and thus a less sustainable way of introducing a new treatment. Early implementation of rigorous and comparative research during a drug's lifecycle could enhance its position and credibility within a specific treatment hierarchy.

Conclusion

The continued availability of UPA for women with symptomatic uterine fibroids could have been valuable, it is, however, no longer authorized in most countries. After two marketing suspensions, leading to indication restriction, placing warning labels and putting in place stringent risk minimization measures, usage of UPA treatment for symptomatic

fibroids strongly declined. This eventually led to the recent voluntary marketing authorization withdrawal of UPA. However, it is critical to recognize that the potential risk of DILI due to UPA was low at 13.5:100.000 and serious DILI leading to liver transplantation was exceedingly rare, with an incidence of about 1 in 200,000 patients. While idiosyncratic DILI is a complex and challenging adverse event to study, regulatory measures, particularly the regular liver functions tests, have not been empirically validated, and may not effectively prevent DILIs. Importantly, alternative treatment methods for symptomatic uterine fibroids may pose even higher mortality and morbidity risks. Moreover, other medications with higher risks of DILI are subject to less stringent liver test assessments.

The case of UPA demonstrates several knowledge gaps and lessons learned. There is a clear need for a better understanding of DILI mechanisms and DILI causality assessment to aid clinical decision making as well as regulatory bodies to correctly identify the true incidence of a drug-related DILI. The current strategy presents challenges in accurately assessing the true DILI risk of a drug, as it heavily depends on spontaneous reporting of suspected adverse events, which often suffer from substantial missing data and rely on a diagnosis by exclusion. Consequently, regulatory bodies may adopt an overly cautious approach in their conclusion and introduce risk-mitigation strategies that could potentially hinder further research. While it is important that a thorough risk-benefit analysis is done to evaluate a drug's potential risks as compared to those of alternative treatment options, an early implementation of comparative research trials would enhance the understanding of the risk-benefit profile. It is unfortunate that a drug with a potentially unique role in treating uterine fibroids is no longer available as a treatment option due to the occurrence of rare cases of DILI.

Abbreviations

CHMP, Committee for Medicinal Products for Human Use; DILI, drug induced liver injury; EMA, European medicines agency; ETASU, Elements to Assure Safety Use; EU, European Union; GnRHa, Gonadotropin-Releasing Hormone agonist; IUD, intra uterine device; LFT, liver function tests; PRAC, pharmacovigilant risk assessment committee; QoL, Quality of Life; RCT, randomized controlled trial; REMs, Risk Evaluation and Mitigation Strategies; RMP, risk management plan; RMM, risk minimisation measures; RUCAM, Roussel Uclaf Causality Assessment Method; SMQ, Standard Sets of MeDRA UPA, Ulipristal Acetate.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

A. Semmler, M.E. de Lange, J.P.H. Drenth, P.M. Bet, N.S. Vermeer report no conflicts of interest in this work.

W.J.K Hehenkamp has received two grants related to the subject of this manuscript. The first grant was received by Gedeon Richter (the manufacturer of UPA) for an investigator initiated randomized trial on UPA versus GnRH agonists prior to a laparoscopic myomectomy. This was before the indication as pretreatment was banned because of the safety measures related to liver injury. The manufacturer was not involved in the conduct of the trial, analysis of the data nor writing of the manuscript. The results were allowed to be published irrespective of the outcome. The second grant was a governmental grant to conduct the RCT on UPA versus standard surgical treatment for symptomatic uterine fibroids. This trial is ongoing (recruitment was completed in November 2024). The above-mentioned grants were exclusively for research, no personal financial benefits applied. There have been no other ties to the manufacturer other than the single grant mentioned above.

J.A.F. Huirne reports payments from Samsung to the institution to cover travel expenses for lectures about imaging on an international congress; payment from Olympus to the institution for expenses for a lecture on an international course on minimal invasive surgery and the following research grants: from Samsung, payment to the institution, for research on imaging of uterine disorders; from Plantec Medical, payment to institution for research on adhesion barrier during

surgery, and a grant from NWO (Dutch research organization), payment to institution for research. Stakeholder Ikherstel, e-health intervention on recovery after surgery.

References

1. Stewart E, Cookson C, Gandolfo R, Schulze-Rath R. Epidemiology of uterine fibroids: a systematic review. *BJOG*. 2017;124(10):1501–1512. doi:10.1111/1471-0528.14640
2. Gupta S, Jose J, Manyonda I. Clinical presentation of fibroids. *Best Pract Res Clin Obstet Gynaecol*. 2008;22(4):615–626. doi:10.1016/j.bpobgyn.2008.01.008
3. Donnez J, Donnez O, Matule D, et al. Long-term medical management of uterine fibroids with ulipristal acetate. *Fertil Steril*. 2016;105(1):165–73.e4. doi:10.1016/j.fertnstert.2015.09.032
4. Donnez J, Hudecek R, Donnez O, et al. Efficacy and safety of repeated use of ulipristal acetate in uterine fibroids. *Fertil Steril*. 2015;103(2):519–27.e3. doi:10.1016/j.fertnstert.2014.10.038
5. Donnez J, Tatarchuk TF, Bouchard P, et al. Ulipristal acetate versus placebo for fibroid treatment before surgery. *N Engl J Med*. 2012;366(5):409–420. doi:10.1056/NEJMoa1103182
6. Donnez J, Vázquez F, Tomaszewski J, et al. Long-term treatment of uterine fibroids with ulipristal acetate ☆. *Fertil Steril*. 2014;101(6):1565–73.e1–18. doi:10.1016/j.fertnstert.2014.02.008
7. Donnez J, Tomaszewski J, Vázquez F, et al. Ulipristal acetate versus leuprolide acetate for uterine fibroids. *N Engl J Med*. 2012;366(5):421–432. doi:10.1056/NEJMoa1103180
8. Murji A, Whitaker L, Chow TL, Sobel ML. Selective progesterone receptor modulators (SPRMs) for uterine fibroids. *Cochrane Database Syst Rev*. 2017;4(4):Cd010770. doi:10.1002/14651858.CD010770.pub2
9. Yin X, He L, Xu H, et al. Efficacy and safety of different doses of mifepristone in the treatment of uterine fibroids: a meta-analysis. *Eur J Obstet Gynecol Reprod Biol*. 2024;303:302–309. doi:10.1016/j.ejogrb.2024.10.059
10. EMA. Assessment Report on Temporary Measures. 2020. Available from: https://www.ema.europa.eu/en/documents/referral/ulipristal-acetate-5mg-medicinal-products-article-31-referral-chmp-scientific-conclusions-prac_en.pdf. Accessed June 10, 2024.
11. Strand T, Kives S, Leyland N, Ashkenas J, Janiszewski P, Thiel J. Treatment choices in a National Cohort of Canadian women with symptomatic uterine fibroids. *J Obstet Gynaecol Can*. 2020;42(12):1475–82.e2. doi:10.1016/j.jogc.2020.06.012
12. Middelkoop MA, Bet PM, Drenth JPH, Huirne JAF, Hehenkamp WJK. Risk–efficacy balance of ulipristal acetate compared to surgical alternatives. *Br J Clin Pharmacol*. 2021;87(7):2685–2697. doi:10.1111/bcp.14708
13. Middelkoop MA, de Lange ME, Clark TJ, et al. Evaluation of marketing authorization and clinical implementation of ulipristal acetate for uterine fibroids. *Hum Reprod*. 2022;37(5):884–894. doi:10.1093/humrep/deac009
14. Kyeong HK, Choi J, Na YJ, Kim HG. Effects of long-term intermittent pharmacological therapy with ulipristal acetate on reducing the volume of uterine fibroids and relieving symptoms. *Minerva Obstet Gynecol*. 2023;75(3):236–242. doi:10.23736/S2724-606X.23.05197-7
15. Morgante G, Centini G, Troìa L, Orvieto R, De Leo V. Ulipristal acetate before in vitro fertilization: efficacy in infertile women with submucous fibroids. *Reprod Biol Endocrinol*. 2020;18(1):50. doi:10.1186/s12958-020-00611-1
16. Shah N, Egbase E, Sideris M, Odejinmi F. What happens after randomised controlled trials? Uterine fibroids and ulipristal acetate: systematic review and meta-analysis of "real-world" data. *Arch Gynecol Obstetrics*. 2021;303(5):1121–1130. doi:10.1007/s00404-020-05918-3
17. Middelkoop MA, Huirne JAF, van der MCJ, Bosmans JE, Hehenkamp WJK. A multi-centre, randomized, non-inferiority trial to compare ulipristal with standard surgical treatment in women with symptomatic uterine fibroids: protocol of the MYOMEX-2 trial. *Eur J Obstet Gynecol Reprod Biol*. 2021;256:63–69. doi:10.1016/j.ejogrb.2020.10.058
18. Clinical Trials Register. Ulipristal versus standard surgical treatment in symptomatic uterine fibroids. EudraCT identifier:2017-005120-16. 20-08-2018. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2017−005120-16/NL. Accessed June 27, 2024.
19. Bello M M-D, González-Bermejo D, Castillo-Cano B, Rodriguez-Pascual A, Montero-Corominas D. Impact of regulatory interventions on ulipristal acetate 5 mg (Esmya) use in Spain: an interrupted time-series analysis. *Pharmacoepidemiol Drug Saf*. 2024;33(9):e70004. doi:10.1002/pds.70004
20. Mathias T. FDA declines to approve Allergan's Esmya: Reuters. 21-08-2018. Available from: https://www.reuters.com/article/idUSKCN1L6268/. Accessed June 27, 2024.
21. EPsEWotmaitEU. https://www.ema.europa.eu/en/documents/public-statement/public-statement-esmya-withdrawal-marketing-authorisation-european-union_en.pdf. Accessed January 31, 2025.
22. Donnez J, Arriagada P, Marciniak M, Larrey D. Liver safety parameters of ulipristal acetate for the treatment of uterine fibroids: a comprehensive review of the clinical development program. *Expert Opin Drug Saf*. 2018;17(12):1225–1232. doi:10.1080/14740338.2018.1550070
23. Regev A, Björnsson ES. Drug-induced liver injury: morbidity, mortality, and Hy's Law. *Gastroenterology*. 2014;147(1):20–24. doi:10.1053/j.gastro.2014.05.027
24. CHMP. Assessment Report Esmya. 2018. https://www.ema.europa.eu/en/documents/assessment-report/esmya-epar-public-assessment-report_en.pdf. Accessed June 10, 2024.
25. CHMP. Assessment Report Esmya. 2015. https://www.ema.europa.eu/en/documents/variation-report/esmya-h-c-2041-ii-0028-epar-assessment-report-variation_en.pdf. Accessed June 10, 2024.
26. EMA. Assessment report. 2018. https://www.ema.europa.eu/en/documents/variation-report/esmya-h-c-2041-a20-0043-epar-assessment-report-article-20_en.pdf. Accessed June 10, 2024.
27. Kang S, Brinker A, Jones SC, Dimick-Santos L, Avigan MI. An evaluation of postmarketing reports of serious idiosyncratic liver injury associated with ulipristal acetate for the treatment of uterine fibroids. *Drug Saf*. 2020;43(12):1267–1276. doi:10.1007/s40264-020-00960-1
28. Dinis-Oliveira RJ, Vieira DN. Acute liver failure requiring transplantation: a possible link to ulipristal acetate treatment? *Basic Clin Pharmacol Toxicol*. 2021;129(3):278–282. doi:10.1111/bcpt.13631
29. Meunier L, Meszaros M, Pageaux GP, et al. Acute liver failure requiring transplantation caused by ulipristal acetate. *Clin Res Hepatol Gastroenterol*. 2020;44(3):e45–e9. doi:10.1016/j.clinre.2020.02.008

30. EMA. Scientific conclusion. 2020. https://www.ema.europa.eu/en/documents/scientific-conclusion/esmya-epar-scientific-conclusions-annex-iv_en.pdf. Accessed June 10, 2024.
31. Carballo-Folgoso L, Alvarez-Navascués C, Rodriguez M. Acute liver failure associated with ulipristal acetate: a case report. *Am J Gastroenterol*. 2020;115(9):1542–1544. doi:10.14309/ajg.0000000000000756
32. Irahara M, Maejima Y, Shinbo N, Yamauchi Y, Mizunuma H. Ulipristal acetate for Japanese women with symptomatic uterine fibroids: a double-blind, randomized, Phase II dose-finding study. *Reprod Med Biol*. 2020;19(1):65–74. doi:10.1002/rmb2.12304
33. Westhoff CL, Archer DF, Barnhart K, et al. Evaluation of ovulation and safety outcomes in a multi-center randomized trial of three 84 day ulipristal acetate regimens. *Contraception*. 2022;112:54–60. doi:10.1016/j.contraception.2022.04.002
34. Illingworth BJG, Hirsch M, Duffy JMN. Ulipristal acetate for treatment of symptomatic uterine leiomyomas: a randomized controlled trial. *Obstetrics Gynecol*. 2018;132(1):215. doi:10.1097/AOG.0000000000002718
35. Liu JH, Soper D, Lukes A, et al. Ulipristal acetate for treatment of uterine leiomyomas: a randomized controlled trial. *Obstet Gynecol*. 2018;132(5):1241–1251. doi:10.1097/AOG.0000000000002942
36. Osuga Y, Nakano Y, Yamauchi Y, Murakawa H. Phase III long-term study to evaluate the efficacy and safety of ulipristal acetate in Japanese patients with uterine fibroids. *J Obstet Gynaecol Res*. 2021;47(9):3269–3278. doi:10.1111/jog.14802
37. Osuga Y, Nakano Y, Yamauchi Y, Takanashi M. Ulipristal acetate compared with leuprorelin acetate for Japanese women with symptomatic uterine fibroids: a phase III randomized controlled trial. *Fertil Steril*. 2021;116(1):189–197. doi:10.1016/j.fertnstert.2021.01.023
38. Fernandez H, Schmidt T, Powell M, Costa APF, Arriagada P, Thaler C. Real world data of 1473 patients treated with ulipristal acetate for uterine fibroids: premya study results. *Eur J Obstetrics Gynecol Reprod Biol*. 2017;208:91–96. doi:10.1016/j.ejogrb.2016.11.003
39. Gracia M, Alcalà M, Ferreri J, et al. Ulipristal acetate improves clinical symptoms in women with adenomyosis and uterine myomas. *J MinInvas Gynecol*. 2018;25(7):91–96. doi:10.1016/j.jmig.2018.04.002
40. Verguts J, Godin PA, De Vree B, et al. Effect on surgical decisions: ulipristal acetate as key player in Belgian Phase IV registration trial. *Int J Gynaecol Obstet*. 2019;147(3):339–343. doi:10.1002/ijgo.12968
41. Giarrè G, Franchini M, Castellacci E, et al. Ulipristal acetate in symptomatic uterine fibroids. A real-world experience in a multicentric Italian study. *Gynecol Endocrinol*. 2020;36(2):171–174. doi:10.1080/09513590.2019.1648419
42. Águas F, Guerreiro F, Ponte C, et al. Management of symptomatic uterine fibroids with ulipristal acetate: a retrospective, multicentric and nationwide study. *J Gynecol Obstet Hum Reprod*. 2020;49(8):101862. doi:10.1016/j.jogoh.2020.101862
43. De Milliano I, Middelkoop MA, Huirne JAF, et al. Ulipristal acetate versus gonadotropin-releasing hormone agonists prior to laparoscopic myomectomy (MYOMEX trial): long term results of a double-blind randomized controlled trial. *Eur J Obstet Gynecol Reprod Biol*. 2020;252:256–264. doi:10.1016/j.ejogrb.2020.06.035
44. Yoon EL, Yuk JS. Use of ulipristal acetate and risk of liver disease: a nationwide cohort study. *J Clin Endocrinol Metab*. 2021;106(6):1773–1782. doi:10.1210/clinem/dgab081
45. Neri M, Pilloni M, Paoletti AM, et al. Repeated two cycles of ulipristal acetate treatment improve the quality of life in premenopausal women with heavy menstrual bleeding dependent on uterine myomas, without impairment of bone health. *Gynecol Endocrinol*. 2019;35(9):756–761. doi:10.1080/09513590.2019.1576618
46. Del Forno S, Degli Esposti E, Salucci P, et al. Liver function, tolerability and satisfaction during treatment with ulipristal acetate in women with fibroids: a single center experience. *Gynecol Endocrinol*. 2020;36(5):445–447. doi:10.1080/09513590.2019.1680626
47. Jha S, Ahmed N, Sinha HH. Safety and efficacy of two repeated cycles of ulipristal acetate in the management of symptomatic uterine fibroid among Indian women. *Prz Menopauzalny*. 2021;20(3):127–132. doi:10.5114/pm.2021.109509
48. Whitaker LHR, Middleton LJ, Daniels JP, et al. Ulipristal acetate versus levonorgestrel-releasing intrauterine system for heavy menstrual bleeding (UCON): a randomised controlled phase III trial. *EClinicalMedicine*. 2023;60:101995. doi:10.1016/j.eclinm.2023.101995
49. Simon JA, Catherino W, Segars JH, et al. Ulipristal acetate for treatment of symptomatic uterine leiomyomas: a randomized controlled trial. *Obstet Gynecol*. 2018;131(3):431–439. doi:10.1097/AOG.0000000000002462
50. Hong YH, Han SJ, Lee D, Kim SK, Jee BC. Adverse symptoms during short-term use of ulipristal acetate in women with uterine myomas and/or adenomyosis. *J Obstet Gynaecol Res*. 2019;45(4):865–870. doi:10.1111/jog.13917
51. Sgro C, Clinard F, Ouazir K, et al. Incidence of drug-induced hepatic injuries: a French population-based study. *Hepatology*. 2002;36(2):451–455. doi:10.1053/jhep.2002.34857
52. Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. *Gastroenterology*. 2013;144(7):1419–25.e3. doi:10.1053/j.gastro.2013.02.006
53. Suk KT, Kim DJ, Kim CH, et al. A prospective nationwide study of drug-induced liver injury in Korea. *Off J Ame College Gastroenterol*. 2012;107(9).
54. European Medicines Agency. EudraVigilance Database [Internet]. Available from: https://www.adrreports.eu/en/search_subst.html#. Accessed 27 Jun 2024.
55. European Medicines Agency. Minutes of PRAC meeting on 26-29 September 2022 [Internet]. 2022 Sep 26-29. Available from: https://www.pharmya.com/wp-content/uploads/2023/02/EU-Minutes-of-PRAC-meeting-on-26-29-September-2022.pdf. Accessed 2024 Jun 27.
56. National Institutes of Health (NIH). Non-interventional study to evaluate long term safety, prescription management patterns of esmya in a long term setting (Premium). NCT02748460. Available from: https://clinicaltrials.gov/study/NCT02748460. Accessed 2024 Jun 27.
57. National Institutes of Health (NIH). A multicenter prospective non-interventional study assessing the management of Canadian women with uterine fibroids. NCT02580578. Available from: https://clinicaltrials.gov/study/NCT02580578. Accessed 2024 Jun 27.
58. National institutes of health (NIH). observation of long-term effects on endometrium and uterine fibroids in women with ulipristal acetate therapy. NCT03972917. Available from https://clinicaltrials.gov/study/NCT03972917#study-record-dates. Accessed 2024 Jun 27.
59. Marquez L, Raheja R, Chan-Liston M, et al. Industry review of best practices for risk management of drug-induced liver injury from development to real-world use. *Drug Saf*. 2024;47(1):1–22. doi:10.1007/s40264-023-01360-x
60. European Association for the Study of the Liver. EASL clinical practice guidelines: drug-induced liver injury. *J Hepatol*. 2019;70(6):1222–1261. doi:10.1016/j.jhep.2019.02.014
61. Izquierdo L, Canivet CM, De Martin E, et al. Investigation of inherited chromosomally integrated human herpesvirus-6A+ and −6B+ in a patient with ulipristal acetate-induced fulminant hepatic failure. *Viruses*. 2021;14(1):62. doi:10.3390/v14010062
62. Nicoletti P, Dellinger A, Li YJ, et al. Identification of reduced ERAP2 expression and a novel HLA allele as components of a risk score for susceptibility to liver injury due to amoxicillin-clavulanate. *Gastroenterology*. 2023;164(3):454–466. doi:10.1053/j.gastro.2022.11.036

63. Monshi MM, Faulkner L, Gibson A, et al. Human leukocyte antigen (HLA)-B*57:01-restricted activation of drug-specific T cells provides the immunological basis for flucloxacillin-induced liver injury. *Hepatology*. 2013;57(2):727–739. doi:10.1002/hep.26077
64. Daly AK. Genetics of drug-induced liver injury: current knowledge and future prospects. *Clin Transl Sci*. 2023;16(1):37–42. doi:10.1111/cts.13424
65. Boudes PF. Risk evaluation and mitigation strategies (REMSs): are they improving drug safety? A critical review of REMSs requiring elements to assure safe use (ETASU). *Drugs R D*. 2017;17(2):245–254. doi:10.1007/s40268-017-0175-y
66. Chalasani N, Fontana RJ, Bonkovsky HL, et al. Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. *Gastroenterology*. 2008;135(6):1924–34,34.e1–4. doi:10.1053/j.gastro.2008.09.011
67. Andrade RJ, Lucena MI, Fernández MC, et al. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. *Gastroenterology*. 2005;129(2):512–521. doi:10.1016/j.gastro.2005.05.006
68. Mylan. Azathioprine tablets 25mg - summary of product characteristics (SmPC). UK: Medicines.org.uk; 2023 updated 2023 Oct 17 Available from: https://www.medicines.org.uk/emc/product/2540/smpc/print. Accessed June 27, 2024.
69. Merck Sharp & Dohme (UK) Limited. Remicade 100mg powder for concentrate for solution for infusion - summary of product characteristics (SmPC). UK: Medicines.org.uk; 2024 updated 2024 Jan 10 Available from: https://www.medicines.org.uk/emc/product/3831/smpc/print. Accessed June 27, 2024.
70. Ennogen Healthcare Ltd. Isotretinoin 20mg Soft capsules - summary of product characteristics (SmPC). UK: Medicines.org.uk; 2023 updated 2023 Nov 1 Available from: https://www.medicines.org.uk/emc/product/10527/smpc/print. Accessed June 27, 2024.
71. ADVANZ Pharma. Nitrofurantoin 100mg capsules - summary of product characteristics (SmPC). UK: Medicines.org.uk; 2024 updated 2024 Feb 7 Available from: https://www.medicines.org.uk/emc/product/428/smpc/print. Accessed June 27, 2024.
72. GlaxoSmithKline UK. Augmentin 625mg tablets - summary of product characteristics (SmPC). UK: Medicines.org.uk; 2024 updated 2024 May 16 Available from: https://www.medicines.org.uk/emc/product/281/smpc/print. Accessed June 27, 2024.
73. Ranbaxy (UK) Limited a Sun Pharmaceutical Company. Atorvastatin 40 mg film-coated tablets - summary of product characteristics (SmPC). UK: Medicines.org.uk; 2023 updated 2023 Oct 19 Available from: https://www.medicines.org.uk/emc/product/4344/smpc/print. Accessed June 27, 2024.
74. Dexcel Pharma Ltd. Diclofenac sodium 50mg gastro-resistant tablets - summary of product characteristics (SmPC). UK: Medicines.org.uk; 2024 updated 2024 Jan 4 Available from: https://www.medicines.org.uk/emc/product/2660/smpc/print. Accessed June 27, 2024.
75. Richter Plc G. Esmya EPAR Product Information. Amsterdam: European Medicines Agency; 2021 updated 2021 Oct 1 Available from: https://www.ema.europa.eu/en/documents/product-information/esmya-epar-product-information_en.pdf. Accessed June 27, 2024.
76. Laine L, Goldkind L, Curtis SP, Connors LG, Yanqiong Z, Cannon CP. How common is diclofenac-associated liver injury? Analysis of 17,289 arthritis patients in a long-term prospective clinical trial. *Am J Gastroenterol*. 2009;104(2):356–362. doi:10.1038/ajg.2008.149
77. National Institute of Diabetes and Digestive and Kidney Diseases. Categorization of the likelihood of drug induced liver injury. In: *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]*. Bethesda (MD): National Library of Medicine; 2012. https://www.ncbi.nlm.nih.gov/books/NBK548392/.
78. Aantal gebruikers 2019-2023 voor ATC-subgroep G03XB02: ulipristal. Nederland/GIP. Available from: https://www.gipdatabank.nl/databank?infotype=g&label=00-totaal&tabel_g_00-totaal=B_01-basis&geg=gebr&spec=vs_gebr&item=G03XB02. Accessed 2024 Jun 27.
79. NHS Business Services Authority. Open Data Portal [Internet]. "ePACT2, NHSBSA Copyright 2024". Available from: https://opendata.nhsbsa.net/. Accessed 27, June 2024.
80. Roth SE, Avigan MI, Bourdet D, et al. Next-generation dili biomarkers: prioritization of biomarkers for qualification and best practices for biospecimen collection in drug development. *Clin Pharmacol Ther*. 2020;107(2):333–346. doi:10.1002/cpt.1571
81. Weber S, Benesic A, Ishigami M, Gerbes AL. Drug-induced liver injury by checkpoint inhibitors: benefit of a causality assessment tool. *Hepatol Commun*. 2020;4(10):1552–1554. doi:10.1002/hep4.1565
82. Benesic A, Leitl A, Gerbes AL. Monocyte-derived hepatocyte-like cells for causality assessment of idiosyncratic drug-induced liver injury. *Gut*. 2016;65(9):1555–1563. doi:10.1136/gutjnl-2015-309528
83. Aithal GP. Pharmacogenetic testing in idiosyncratic drug-induced liver injury: current role in clinical practice. *Liver Int*. 2015;35(7):1801–1808. doi:10.1111/liv.12836
84. Zhang GY, Rubin JB. Rethinking drug-induced liver injury—A New era of pharmacovigilance. *JAMA Intern Med*. 2024;184(8):952–953. doi:10.1001/jamainternmed.2024.1833
85. Ferrero S, Vellone VG, Barra F. Pharmacokinetic drug evaluation of ulipristal acetate for the treatment of uterine fibroids. *Expert Opin Drug Metab Toxicol*. 2018;14(1):107–116. doi:10.1080/17425255.2018.1417389
86. Langhammer AJ, Nilsen OG. In vitro inhibition of human CYP1A2, CYP2D6, and CYP3A4 by six herbs commonly used in pregnancy. *Phytother Res*. 2014;28(4):603–610. doi:10.1002/ptr.5037
87. Lilja JJ, Kivistö KT, Neuvonen PJ. Duration of effect of grapefruit juice on the pharmacokinetics of the CYP3A4 substrate simvastatin. *Clin Pharmacol Ther*. 2000;68(4):384–390. doi:10.1067/mcp.2000.110216
88. Amoah A, Joseph N, Reap S, Quinn SD. Appraisal of national and international uterine fibroid management guidelines: a systematic review. *Bjog*. 2022;129(3):356–364. doi:10.1111/1471-0528.16928