12 November 2020
EMA/524073/2020
Committee for Medicinal Products for Human Use (CHMP)
Pharmacovigilance Risk Assessment Committee (PRAC)

Ulipristal acetate 5mg

Procedure number: EMEA/H/A-31/1496

Esmya EMEA/H/A-31/1496/C/2041/0049

Ulipristal Acetate Gedeon Richter EMEA/H/A-31/1496/C/5017/0002

CHMP scientific conclusions and PRAC Assessment report of the Review under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

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1. Scientific conclusions and CHMP's detailed explanation on the scientific grounds for the differences with the PRAC recommendation

Note

Scientific conclusions as adopted by the CHMP with all information of a commercially confidential nature deleted.

Scientific conclusions and CHMP detailed explanation of the scientific grounds for the differences with the PRAC recommendation

Ulipristal acetate 5mg (Esmya) was first authorised in all EU/EEA countries on 23 February 2012 via a centralised procedure. Since 2019, generic ulipristal acetate 5mg medicines have been authorised via national procedures in several EU countries under various trade names. The post-marketing exposure of ulipristal acetate 5mg was estimated at 960,414 patients, cumulatively up to 29 February 2020.

Ulipristal acetate was granted EU Marketing Authorisation initially for pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age with a treatment course duration limited to 3 months due to the absence of long-term safety data for a period longer than 3 months. When long-term data became available, a second indication was approved in 2015 to allow repeated intermittent treatment courses in women who were not planned to undergo surgery.

In May 2018, PRAC finalised a review of the benefit-risk balance of Esmya under Article 20 of Regulation (EC) No 726/2004, initiated due to the reporting of three cases of serious liver injury leading to liver transplantation. During the review, an additional case was reported regarding an acute liver failure associated with the use of ulipristal acetate 5mg. As outcome of the review, and taking all data available into consideration, PRAC recommended a set of measures to minimise the risk of serious liver injury associated with ulipristal acetate 5mg including restrictions of the indications. The PRAC recommendations were endorsed by the CHMP in May 2018. Ulipristal acetate is currently approved in the EU/ EEA for the following indications:

- *one treatment course* of pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.
- intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age who are *not eligible for surgery*.

In December 2019, EMA was informed of a new case of serious liver injury leading to liver transplantation following exposure to ulipristal acetate (5th case cumulatively).

The seriousness of the case reported, the causal relationship between ulipristal acetate 5mg and acute liver failure, and its occurrence despite adherence to implemented risk minimisation measures were considered of major concern warranting an in-depth investigation of the impact on the benefit-risk balance of ulipristal acetate and further consideration of the effectiveness of the implemented risk minimisation measures.

On 5 March 2020, the European Commission (EC) initiated a procedure under Article 31 of Directive 2001/83/EC and requested the Agency to assess the above concerns and their impact on the benefit-risk balance of ulipristal acetate 5mg and to give its opinion, on whether the marketing authorisation for ulipristal acetate 5mg should be maintained, varied, suspended or revoked. The EC also requested the Agency to give its opinion as to whether provisional measures were necessary.

On 12 March 2020, after review of the available data and in particular the 5th cumulative case of serious liver injury leading to liver transplantation, the PRAC recommended, as a temporary measure, the suspension of the marketing authorisations of ulipristal acetate 5 mg medicinal products until a definitive decision could be reached.

The PRAC adopted a recommendation on 3 September 2020 to revoke the marketing authorisation of the concerned products which was considered by the CHMP, in accordance with Article 107k of Directive 2001/83/EC.

Overall summary of the scientific evaluation by the PRAC

The efficacy of ulipristal acetate 5mg in the treatment of symptoms of uterine fibroids has been demonstrated at the time of the initial marketing authorisation of Esmya. The clinical benefits of the pre-operative treatment could be considered limited as it is restricted to one treatment course prior to surgery, and there are other short-term treatment alternatives. The benefits of ulipristal acetate are considered largest in the intermittent treatment indication, i.e. for patients who are not eligible for surgery, since for those patients treatment alternatives are limited. Those who are not eligible for surgery may include women who, for various reasons, constitute a surgical risk, such as being obese, suffering from concurrent disease, being treated with certain medications or wanting to preserve fertility. Thus, ulipristal acetate 5mg may provide clinically relevant benefits to women who are not eligible for surgery, whose health and quality of life are affected by symptoms of uterine fibroids, in particular heavy bleeding.

The risk of drug induced liver injury (DILI) in association with use of ulipristal acetate 5mg has been reviewed thoroughly in the previous Article 20 review of Esmya. As outcome of this review, `hepatic failure´ was adjudicated as an adverse drug reaction and DILI as an important identified risk for ulipristal acetate, both approved indications were restricted, and several risk minimisation measures were implemented. In addition, the MAH of Esmya was requested to perform several studies including on the mechanism of ulipristal acetate associated liver injury to further characterise this risk. However these studies have not contributed to further elucidate the mechanism of liver injury in association with ulipristal acetate 5mg and based on the available evidence, the hepatotoxicity associated with ulipristal acetate is considered to be of an idiosyncratic nature, making it difficult to identify susceptible patients who would be at an increased risk.

Since the previous review, Gedeon Richter noted that the patient exposure to Esmya had registered a significant decrease (over 50%). Between 1 March 2018 and 29 February 2020, 476 new cases were received within the hepatic disorder SMQ (serious and non-serious events); of those, 97 cases were serious with 7 cases containing sufficient/partially sufficient information for causality assessment, including one case of serious liver injury leading to liver transplantation (5th cumulative case). For this case, no confounding factors were identified, and other plausible aetiologies were ruled out; consequently, causality between ulipristal acetate and acute hepatitis leading to acute liver failure and liver transplantation was assessed as probable/highly probable, i.e. with a considerably higher degree of certainty.

It was also noted that a progression in the development of hepatic failure leading to liver transplantation could not be prevented. This case therefore confirms that the recommendations for liver monitoring as included in the product information further to the previous referral were not able to prevent serious liver injury leading to liver transplantation in all patients.

In the context of this review, the MAHs were asked to discuss the need and feasibility for any further risk minimisation measures to further mitigate the risk of serious liver toxicity, including changes to the product information, as well as proposals to monitor their effectiveness.

To further minimise the risk, the MAH of the originator product Esmya has proposed to withdraw the indication for pre-operative treatment, indicating that, the pre-operative treatment could be replaced by the use of a GnRH agonist for short-term use. As pointed out by some experts consulted in the context of this review, the reduction of volume of fibroids by ulipristal acetate 5mg is not considered very high and thus the use of this product in the pre-operative setting does not profoundly impact the success of surgery. It was also noted by most experts that alternatives exist for this indication in the pre-operative stage. In view of the above and taking into account the risk of serious liver injury leading to liver transplantation with ulipristal acetate 5mg, the benefit-risk balance of ulipristal acetate 5mg in

the pre-operative treatment of moderate to severe symptoms of uterine fibroids is considered unfavourable for this indication and this indication should therefore be removed.

To further minimise the risk, the MAH of Esmya also proposed a restriction of the target population for the intermittent indication to patients *not eligible for hysterectomy.* However, concerns were raised on the definition of this subset of patients. From the discussions in the expert group convened in the context of this review, it became apparent that the proposed description/definition of this subset of patients appears very broad (e.g. women with apparent medical contraindications for surgery, women having failed other treatment options, women wanting to preserve fertility, and women not willing to undergo surgery). Depending on the interpretation in clinical practice of "patients not willing to undergo surgery" or "patients not suitable for surgery/hysterectomy", this indication may apply to many patients thus rendering the restriction of the indication to "not eligible to surgery/ hysterectomy" weak as a risk minimisation measure. The experts also recognised that data on the benefits of ulipristal acetate 5mg beyond symptom relief, i.e. avoiding surgery/hysterectomy in the longer term are currently lacking.

The experts consulted during the review recommended that the benefits and risks of ulipristal acetate should be sufficiently communicated to the patients – most importantly the risk of liver injury – and stressed the importance of placing those benefits and risks in the context of the benefits and risks of all other available options. The PRAC considered the reflections from the experts that surgical treatment alternatives to treat moderate to severe symptoms of uterine fibroids are not without risk. However, PRAC considered that making a fair comparison between surgical and pharmacological treatments was challenging as it would have to include different kinds of short- and long-term outcomes on health by either treatment, preferably based on comparative studies. Surgical treatment can lead to immediate cure but may convey, in rare cases, a risk of short- or long-term sequelae, whereas pharmacological treatments mainly result in alleviation of symptoms but, in rare instances, may lead to serious adverse events. Gedeon Richter, the MAH of Esmya, also acknowledged that the feasibility of ensuring that all patients have equal opportunity to make an adequately informed decision, including appropriate information sharing by the treating physician regarding the risks of treatment options and its relevant consequences, should be considered, and that based on the available tools and communication channels, significant limitations could be identified.

PRAC was of the view that the proposed changes to the indications (i.e., removal of the preoperative indication and restriction of the intermittent indication to *not eligible to surgery/hysterectomy*) may further reduce the number of patients exposed to ulipristal acetate 5mg. However, as acknowledged by the MAH of Esmya, the patient group for whom the therapy is suitable cannot be scientifically well defined, which would make the decision of treatment with ulipristal acetate 5mg rather subjective. In addition, in view of the idiosyncratic nature of the risk and the difficulty to predict its occurrence (e.g., by identifying relevant risk factors), the PRAC considered that the risk of severe liver injury would not be sufficiently reduced in those who would still be exposed. The experts consulted also could not identify a population where the risk could be predicted and therefore prevented. PRAC also noted the feasibility limitations of ensuring adequate information is made available to all patients for an informed decision and was of the view that no further risk minimisation measures could be implemented that would prevent the risk of severe liver injury. In view of the above, PRAC concluded that the benefit-risk balance of ulipristal acetate 5mg was unfavourable as intermittent treatment of moderate to severe symptoms of uterine fibroids.

In view of the seriousness and idiosyncratic nature of the risk of serious liver injury, the occurrence of hepatic failure despite the implemented risk minimisation measures, that neither further risk measures to prevent and reduce the risk was identified nor a sub-population where the benefit risk balance of ulipristal 5mg could be positive, the PRAC concluded that this risk outweighs the benefits of ulipristal

acetate 5mg in all its indications. As no condition, if fulfilled in the future, would demonstrate a positive benefit-risk balance for these products, the PRAC recommended the revocation of the marketing authorisations for ulipristal acetate 5mg medicinal products.

Grounds for PRAC recommendation

Whereas

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC resulting from the evaluation of data from pharmacovigilance activities, for ulipristal acetate 5mg medicinal products;
- The PRAC reviewed the information available to the Committee on ulipristal acetate 5mg and the risk of serious liver injury, including the data provided by the marketing authorisation holders of ulipristal acetate 5mg in writing and in oral explanations and the outcome of the consultation with the ad-hoc expert group convened in the context of this procedure;
- The PRAC reviewed all cases of serious liver injury reported among women treated with ulipristal acetate 5 mg for the treatment of symptoms of uterine fibroids, including a new case of serious liver injury leading to liver transplantation (the 5th case cumulatively) reported although the risk minimisation measures agreed as outcome of the previous Article 20 referral were followed. The PRAC concluded that the causal association of ulipristal acetate 5mg with serious liver injury was probable/highly probable and noted that a progression in the development of hepatic failure leading to liver transplantation could not be prevented;
- The PRAC discussed further risk minimisation proposals and could not identify any additional measures that would ensure effective minimisation of the risk to an acceptable level. In view of the seriousness and idiosyncratic nature of the risk, the PRAC concluded that this risk outweighs the benefits of ulipristal acetate 5mg in the treatment of the symptoms of uterine fibroids. No sub-group of patients in which the benefits of ulipristal acetate 5mg would outweigh the risks could be identified;
- Furthermore, the PRAC could not identify any condition, the fulfilment of which would demonstrate a positive benefit-risk balance of ulipristal acetate 5mg medicinal products.

The Committee, as a consequence, considers that the benefit-risk balance of ulipristal acetate 5mg medicinal products for the treatment of symptoms of uterine fibroids is not favourable and recommends, pursuant to Article 116 of Directive 2001/83/EC, the revocation of the marketing authorisations of all ulipristal acetate 5mg medicinal products.

CHMP detailed explanation of the scientific grounds for the differences from the PRAC recommendation

The CHMP considered the PRAC recommendation and the additional information provided by the MAHs as well as the outcome of the consultation with the ad-hoc expert group convened in the context of this procedure. Based on these data, the CHMP did not agree with the PRAC overall conclusions and grounds for recommendation.

Points of divergence with the PRAC recommendation and scientific rationale of the CHMP position

Safety aspects

The risk of serious liver injury with ulipristal acetate 5mg was assessed in the context of the Article 20 review of Esmya in 2018 and it was concluded by the PRAC and the CHMP that the product may carry a risk for serious liver injury. While uncertainties around causality remained, PRAC and CHMP recognised the very serious outcome of the reported cases of liver injury and a set of risk minimisation measures was implemented for Esmya, including a restriction of indication, the introduction of a contra-indication in patients with underlying liver disorder, a recommendation to perform liver function tests prior and during treatment, and implementation of educational material, including a patient card in each pack of ulipristal acetate 5mg to adequality inform patients about the possible risks of liver injury. With the risk being clearly communicated to patients and healthcare professionals, an expectation was that if more cases of severe liver injury leading to liver injury had occurred, they would be reported then.

An evaluation of the effectiveness of the risk minimisation measures taken in 2018 indicated that the limitation of the population by restricting the two indications had led to a large decrease in number of patients treated to around 25-30% of the proportion of patients prior to the Article 20 referral in 2018. The CHMP noted that the reporting rate of serious liver injury leading to liver transplantation of 0.52/100,000 based on 4/765.000 patients exposed to ulipristal acetate 5mg prior to the previous Article 20 procedure and 0.51/100,000 based on 1/194.614 patients exposed to ulipristal acetate 5mg since the previous Article 20 procedure, remained the same. It was also noted that these incidences are in line a conservative background incidence of death/liver transplantation of 0.55 cases per 100,000 inhabitants as described by Ibañez in 2002[1].

The CHMP also noted that the results in a limited number of patients with increased liver function test results during use of ulipristal acetate 5 mg showed improvement or normalisation of the increased liver function test (LFT) values after discontinuation of ulipristal. Although these data are limited, they suggest that the performance of liver function tests is useful in the prevention of progression of liver damage. CHMP however acknowledged that the 5th case of serious liver injury reported in December 2019 had a probable/highly probable causal relationship with ulipristal acetate 5mg and that this case had occurred despite the risk minimisation measures in place and that a progression in the development of hepatic failure leading to liver transplantation could not be prevented.

Efficacy aspects

- Pre-operative treatment of moderate to severe symptoms of uterine fibroids

At the end of one treatment course (3 months), 73.4% and 75.3%, respectively, of patients in two different phase III studies reported amenorrhoea and the median fibroid volume had been reduced compared to baseline by 21.2% and 35.6%, respectively.

[1] Ibáñez L, Pérez E, Vidal X, Laporte JR; Grup d'Estudi Multicènteric d'Hepatotoxicitat Aguda de Barcelona (GEMHAB). Prospective surveillance of acute serious liver disease unrelated to infectious, obstructive, or metabolic diseases: epidemiological and clinical features, and exposure to drugs. J Hepatol. 2002 Nov;37(5):592-600.

The reduction in myoma size, which may facilitate surgery, as well as reduction in blood loss and anaemia, which will improve the general health of the patient, are considered clinically relevant. However, the clinical benefits of the pre-operative treatment are considered limited, and there is another short-term pre-operative treatment alternative, i.e. a GnRH-agonist.

- Intermittent treatment of moderate to severe symptoms of uterine fibroids

At the end of the fourth treatment course, corresponding to approximately two years of treatment (4 courses of 3 months with re-treatment courses starting in the first week of the second menstruation following the previous treatment course completion), 69.6% of patients reported amenorrhoea and the median reduction of myoma volume from baseline was 71.8% in one phase III study.

The benefits of ulipristal acetate 5 mg are considered largest in the intermittent treatment indication, i.e., for patients whose health and quality of life are affected by symptoms of uterine fibroids, in particular heavy bleeding, but who are not suitable for surgery, since for those patients in need of longer treatment, there are no other obvious pharmacological treatment alternatives. Those who are not suitable for surgery may include women who, for various reasons, present a surgical risk, such as being obese, women at increased risk of venous thrombosis, with a concomitant disease, or receiving concomitant medications. Surgery may also not be suitable for women wanting to preserve the possibility to become pregnant.

Benefit-risk balance

The CHMP noted that the 5th case of serious liver injury reported with ulipristal acetate 5mg has a probable/highly probable causal relationship with ulipristal acetate 5mg and acknowledged that this case had occurred despite the risk minimisation measures in place and that a progression in the development of hepatic failure leading to liver transplantation could not be prevented. However, the CHMP noted that the incidence of serious liver injury leading to liver transplantation with ulipristal acetate 5mg is in line with a conservative background incidence of death/liver transplantation.

The CHMP further considered the proposal from the MAH of Esmya to withdraw the pre-operative treatment indication to limit the exposure to ulipristal acetate and thus further minimising the risk. The indication of one treatment course of pre-operative treatment reflects a situation where surgery is planned, however reductions in myoma size as well as reductions in blood loss and anaemia are considered of clinical significance. However the CHMP noted that some experts consulted in the context of this review had pointed out that the reduction of volume of fibroids by ulipristal acetate 5mg was not considered very high and thus the use of this product in the pre-operative setting did not profoundly impact the success of surgery. The CHMP also noted that the experts had highlighted that alternatives exist for this indication in the pre-operative stage. In view of the above and taking into account the risk of serious liver injury leading to liver transplantation with ulipristal acetate 5mg, the CHMP agreed with the PRAC that ulipristal acetate 5mg should no longer be used as pre-operative treatment of moderate to severe symptoms of uterine fibroids and therefore this indication should be removed.

The CHMP noted that the PRAC was also of the view that the benefit-risk of ulipristal acetate 5mg was negative as intermittent treatment of moderate to severe symptoms of uterine fibroids. The CHMP was however of the opinion that the benefits of ulipristal acetate 5mg in the intermittent treatment indication remain relevant for a subgroup of women with moderate to severe symptoms of uterine fibroids when uterine fibroid embolisation and/or surgical treatment options are not suitable or have failed, since for those patients there are only very limited treatment alternatives.

The experts consulted during an ad hoc expert group (AHEG) meeting agreed that when considering ulipristal acetate 5mg as an intermittent treatment it is very important to take into account the risks related to the alternative options (hysterectomy and the less invasive alternative surgical treatments, such as abdominal myomectomy or intraoperative conversion to hysterectomy). An important aspect to take into account is that each surgical option has its own risk, e.g. the mortality rate after hysterectomy ranges from 1 in 500 to 1 in 3000; while major complications such as bleeding, intestinal perforation are at the frequency of 1 in 100. Recurrence of fibroids after myomectomy is common and additional treatment may be required (American college of Obstetricians and gynaecologists 2008). Abdominal myomectomy also confers substantial risks with respect to fertility, including a 3 to 4% risk of intraoperative conversion to hysterectomy and frequent development of postoperative intra-uterine adhesions. The rates of major complications after embolisation are similar to those after surgery, but embolisation is associated with a higher risk of minor complications and of the need for additional surgical intervention (typically hysterectomy)[2].

The expert group indicated that it is also important to consider the patient population that does not want to undergo surgery, such as younger patients for whom denying hysterectomy would preserve the possibility to become pregnant. In this context, most experts consulted in the context of the ad-hoc expert group meeting stressed the need of having ulipristal acetate 5mg as an option for intermittent treatment of moderate to severe symptoms of uterine fibroids.

It was also noted that the experts had stressed the importance of a detailed analysis of the risks and careful review of the individual case before any decision on the treatment is made and that counselling of patients should be the centre of decision-making. The patient representative present at the meeting shared this opinion, stressing the importance of choice and informed decision of the individuals taking into account all available options.

The CHMP agreed that the decision on whether surgery is the best option, including hysterectomy, should be at the level of the treating physician and the patient in a setting of informed decision making. CHMP was also of the view that, provided that the benefits and risks of ulipristal acetate 5mg and other avaialble treatment options are sufficiently communicated to both the healthcare professionals and the patients, ulipristal acetate 5mg should remain available for intermittent treatment of moderate to severe symptoms of uterine fibroids for adult women who have not reached menopause when uterine fibroid embolisation and/or surgical treatment options are not suitable or have failed.

To further minimise the risks and enhance the communication about the risks associated with ulipristal acetate 5mg, the CHMP recommended that the product information should be updated to reflect that in some cases of liver injury, liver transplantation was required. The CHMP also recommended an update of the educational material for both prescribers and patients to increase awareness about the risk of severe liver injury and highlight the need to counsel patients on the risk and benefits of available treatment options to allow them to take an informed decision.

Summary of the new recommended measures

Amendments to the product information

The CHMP considered that amendments to sections 4.1, 4.4 and 4.8 of the SmPC were necessary to minimise the risk of severe liver injury associated with the use of ulipristal acetate 5mg.

The indication was restricted to intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women who have not reached menopause, when uterine fibroid embolisation and/or

[2] Stewart E. Uterine fibroids. N Engl J Med 2015; 372:1646-1655

surgical treatment options are not suitable or have failed. The indication of one treatment course of pre-operative treatment was deleted as ulipristal acetate 5mg should no longer be used in this indication.

In addition, the warnings and precautions for use section of the product information (section 4.4) as well as the description of hepatic failure adverse reaction in section 4.8 were amended to reflect the fact that some cases of liver injury and hepatic failure reported with ulipristal acetate 5mg required liver transplantation.

The Package Leaflet was amended accordingly.

Additional risk minimisation measures

The MAHs should operate a risk management system described in a revised risk management plan with the following amendments.

The CHMP considered that the existing Physician's guide to prescribing should be amended to reflect the revised indication, the fact that some cases of liver injury and hepatic failure reported with ulipristal acetate 5mg required liver transplantation and highlight that the frequency of hepatic failure and patient risk factors are unknown. Prescribers should also advise patients on the risk and benefits of available treatment options to allow them to take an informed decision.

It was also considered that the existing patient alert card should be amended to clarify that in a small number of cases liver transplantation was necessary.

Direct Healthcare Professional Communication and Communication plan

The Committee adopted the wording of a direct healthcare professional communication (DHPC), to inform healthcare professionals (HCPs) of the outcome of this review, including the restricted indication for ulipristal acetate, provide background information on the risk of severe liver injury, and advise HCPs to inform patients about possible signs and symptoms of liver injury as well as about the risk and benefits of all available alternatives to allow them to take an informed decision. The Committee also agreed on a communication plan.

Grounds for CHMP opinion and for the differences with the PRAC recommendation

Whereas

- The CHMP took into account the PRAC recommendation on ulipristal acetate 5mg and all the data provided by the marketing authorisation holders of ulipristal acetate 5mg;
- The CHMP noted that the causal association of ulipristal acetate 5mg with the 5th case of serious liver injury leading to liver transplantation has been assessed as probable/highly probable, and acknowledged that a progression in the development of hepatic failure leading to liver transplantation could not be prevented although the risk minimisation measures agreed as outcome of the previous Article 20 referral were followed;
- The CHMP agreed that the risk of serious liver injury outweighs the benefits of ulipristal acetate as one treatment course of pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age and this indication should therefore be removed in agreement with the MAHs;
- The CHMP was however of the view that the benefit-risk of ulipristal acetate in the intermittent treatment indication is only considered to remain favourable in a subgroup of women with moderate to severe symptoms of uterine fibroids who have not reached menopause and for who

uterine fibroid embolisation and/or surgical treatment options are not suitable or have failed, subject to the risks being sufficiently communicated to patients and prescribers through wording in the product information and educational material to ensure well-informed treatment decisions in addition to the risk minimisation measures already implemented as outcome of the previous review.

The CHMP, as a consequence, considers that the benefit-risk balance of ulipristal acetate 5mg medicinal products remains favourable subject to the amendments to the product information and additional risk minimisation measures described above.

Therefore, the CHMP recommends the variation to the terms of the marketing authorisations for ulipristal acetate 5mg medicinal products.

Divergent positions to the CHMP opinion

Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure No: EMEA/H/A-31/1496

Esmya EMEA/H/A-31/1496/C/2041/0049

Ulipristal Acetate Gedeon Richter EMEA/H/A-31/1496/C/5017/0002

Ulipristal acetate 5mg

Divergent statement

The undersigned CHMP members consider that the benefit-risk balance for ulipristal acetate 5mg is negative for the following reasons:

- Thus far five cases of serious liver injury requiring liver transplantation have been reported among women treated with ulipristal acetate 5 mg for symptoms of uterine fibroids since approval in 2012; despite an obvious decline in exposure following the Art 20 referral, a 5th case occurred;
- For the most recently reported case, the risk minimisation measures in sections 4.3 and 4.4 of the SmPC, implemented following the Article 20 procedure, were adhered to; thus, the recommendations for liver monitoring included in the SmPC are not sufficient to prevent serious liver injury in all patients;
- As the mechanism behind the risk of DILI associated with the use of ulipristal acetate is unknown, the population "at risk" cannot be further identified;
- Serious liver injury may be life-threatening and when liver transplantation is required, this may result in long-term sequelae and require life-long treatment with immunosuppressants;
- Although symptomatic and affecting the quality of life, moderate to severe symptoms of uterine fibroids are not considered a life-threatening condition;
- For women who are not willing to or eligible for surgery/ hysterectomy other short-term medical treatment options are available.

CHMP Members expressing a divergent opinion:

- Sinan B. Sarac
- Alexandre Moreau
- Christophe Focke
- Jan Mueller-Berghaus
- Jayne Crowe
- Ewa Balkowiec Iskra

- Kristina Dunder
- Martina Weise
- Bruno Sepodes
- Konstantinos Markopoulos
- Armando Genazzani
- Ilko Getov

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- For the most recently reported case, the risk minimisation measures in sections 4.3 and 4.4 of the SmPC, implemented following the Article 20 procedure, were adhered to; thus, the recommendations for liver monitoring included in the SmPC are not sufficient to prevent serious liver injury in all patients;
- As the mechanism behind the risk of DILI associated with the use of ulipristal acetate is unknown, the population "at risk" cannot be further identified;
- Serious liver injury may be life-threatening and when liver transplantation is required, this may result in long-term sequelae and require life-long treatment with immunosuppressants;
- Although symptomatic and affecting the quality of life, moderate to severe symptoms of uterine fibroids are not considered a life-threatening condition;
- For women who are not willing to or eligible for surgery/ hysterectomy other short-term medical treatment options are available.

CHMP Member expressing a divergent opinion:

- Bjorg Bolstad

2. PRAC Assessment report

Note

Assessment report as adopted by the PRAC and considered by the CHMP with all information of a commercially confidential nature deleted, to be read in conjunction with subsequent CHMP scientific conclusions.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

03 September 2020
EMA/524073/2020
Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Invented name(s): Esmya
Ulipristal Acetate Gedeon Richter

Ulipristal acetate 5mg

Procedure number: EMEA/H/A-31/1496

Esmya EMEA/H/A-31/1496/C/2041/0049

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3. Information on the procedure

Ulipristal acetate 5mg (Esmya) was first authorised in all EU/EEA countries on 23 February 2012 via a centralised procedure. Since 2019, generic ulipristal acetate 5mg medicines have been authorised via national procedures in several EU countries under various trade names. The post-marketing exposure of ulipristal acetate 5mg was estimated at 960,414 patients, cumulatively up to 29 February 2020.

Ulipristal acetate was granted EU Marketing Authorisation initially for pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age with a treatment course duration limited to 3 months due to the absence of long-term safety data for a period longer than 3 months. When long-term data became available, a second indication was approved in 2015 to allow repeated intermittent treatment courses in women who were not planned to undergo surgery.

In May 2018, PRAC finalised a review of the benefit-risk balance of Esmya under Article 20 of Regulation (EC) No 726/2004 initiated due to the reporting of three cases of serious liver injury leading to liver transplantation. During the review, an additional case was reported regarding an acute liver failure associated with the use of ulipristal acetate 5mg. As outcome of the review, and taking all data available into consideration, PRAC recommended a set of measures to minimise the risk of serious liver injury associated with ulipristal acetate 5mg including restrictions of the indications. The PRAC recommendations were endorsed by the CHMP in May 2018. Ulipristal acetate is currently approved in the EU/ EEA for the following indications:

- **one treatment course** of pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.
- intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age who are **not eligible for surgery**.

In December 2019, EMA was informed of a new case of serious liver injury leading to liver transplantation following exposure to ulipristal acetate (5^{th} case cumulatively).

The seriousness of the case reported, the causal relationship between ulipristal acetate 5mg and acute liver failure, and its occurrence despite adherence to implemented risk minimisation measures were considered of major concern warranting an in-depth investigation of the impact on the benefit-risk balance of ulipristal acetate and further consideration of the effectiveness of the implemented risk minimisation measures.

On 5 March 2020, the European Commission (EC) initiated a procedure under Article 31 of Directive 2001/83/EC and requested the Agency to assess the above concerns and their impact on the benefit-risk balance of ulipristal acetate 5mg and to give its opinion, on whether the marketing authorisation for ulipristal acetate 5mg should be maintained, varied, suspended or revoked. The EC also requested the Agency to give its opinion as to whether provisional measures were necessary.

The scope of this procedure is limited to ulipristal acetate 5mg indicated as treatment of symptoms of uterine fibroids.

4. Scientific discussion

4.1. Introduction

Uterine fibroids (uterine leiomyoma) are benign, monoclonal, hormone-sensitive, smooth muscle tumours of the uterus in premenopausal women. They are the most common tumour of the female reproductive tract in pre-menopausal women and have been reported to affect 20-40% of women during their reproductive years. Uterine fibroids are often asymptomatic, but when symptomatic, the primary symptoms are fibroid-related bleeding and subsequent anaemia, and abdominal pressure and abdominal pain, increased urinary frequency and infertility related to the volume and location of the tumour. Heavy menstrual blood loss is one of the most frequently disabling symptoms of uterine fibroids.

Uterine fibroids are commonly treated surgically, and symptomatic uterine fibroids are the main reason for hysterectomy. Other less invasive treatment procedures include myomectomy (which may preserve fertility), uterine artery embolisation and, if the dominant symptom is bleeding, endometrial ablation. Surgery may not be a suitable option for all patients, e.g. for medical or personal reasons or if the woman is peri-menopausal and would rather wait for the symptoms of uterine fibroids decrease as a result of entering menopause.

In addition to ulipristal acetate 5mg, symptomatic fibroids may be treated with gonadotropin releasing hormone (GnRH) agonists which are effective in reducing fibroid-related bleeding, reducing abdominal symptoms and reducing fibroid and uterine volume. However, their use is limited to 3-6 months duration as suppression of oestrogen to castration levels leads to loss of bone mineral density and results in menopausal symptoms including hot flushes.

In May 2018, PRAC/CHMP finalised a review of the benefit-risk balance of Esmya under Article 20 of Regulation (EC) No 726/2004 initiated following the reporting of cases of serious liver injury leading to liver transplantation. The review concluded that ulipristal acetate 5mg may carry a risk for serious liver injury. While uncertainties around causality remained, PRAC recognised the very serious outcome of the reported cases of liver injury and taking all data available into consideration, recommended the following measures to minimise the risk of serious liver injury associated with ulipristal acetate 5mg[3]:

- The indications to be restricted to only one treatment course of pre-operative treatment and for intermittent treatment in adult women of reproductive age who are not eligible for surgery;
- A contraindication in patients with underlying hepatic disorder;
- Liver tests to be conducted before, during and after the first two treatment courses;
- Esmya to be discontinued in case of elevated transaminases or symptoms compatible with liver injury.

In December 2019, a new case of serious liver injury leading to liver transplantation following exposure to ulipristal acetate (5th case cumulatively) was reported. Based on the available information at the time, the causal association with the use of ulipristal acetate 5mg was assessed as probable and it was noted that although the risk minimisation measures implemented previously were followed, a progression in the development of hepatic failure leading to liver transplantation could not be prevented.

Taking into account the seriousness of the reported adverse event, the fact that this case occurred despite adherence to the risk minimisation measures in place, and that the approved indication

[3] More information is available in the published assessment report on the Article 20 review for Esmya

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

4.1.1. Safety aspects

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

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

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

Prior to the Article 20 review of Esmya (cut-off date: 28 February 2018), 105 cases had been reported within the Hepatic disorder SMQ, including 33 cases with serious liver disorder SMQ. Among 33 cases, 16 cases were reported with sufficient/partially sufficient information for causality assessment, including 4 cases of acute liver failure leading to liver transplantation. For these 4 cases, reviewed during the Article 20 procedure[5], the causal association between Esmya and serious liver injury was assessed as possible or probable with remaining uncertainty regarding pre-existing liver disease in 2 cases, the role of Human Herpesvirus 6 infection in the third case and a possible role of hepatitis E infection in the fourth case. Generally, the peak time to onset of liver injury was around 140 days and the vast majority of the reported potential drug induced liver injuries occurred between 1 and 8 months (2 treatment cycles including 2 months pause).

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

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

[4] More information is available in the published assessment report on provisional measures
[5] More information is available in the published assessment report on the Article 20 review for Esmya

the initiation of this review, did therefore not add to the current knowledge of ulipristal involvement in the establishment of liver injury. Based on the current knowledge, the hepatotoxicity associated with ulipristal acetate is considered to be of idiosyncratic nature, which makes it difficult to identify susceptible patients who would be at an increased risk.

From 1 March 2018 (the day after the cut-off date of the Article 20 review) until 29 February 2020, 476 new cases were received within the hepatic disorder SMQ (serious and non-serious events); of those, 97 cases were serious with 7 cases containing sufficient/partially sufficient information for causality assessment, including one case of serious liver injury leading to liver transplantation (5th cumulative case). These cases were assessed in the context of this referral procedure and are presented below.

Of note, the reported patient exposure was estimated to be approximately 200,000 to 275,000 patient-years prior to the Article 20 review conducted by the PRAC in 2018 and to approximately 51,000 to 70,000 patient-years after the review and up to February 2020.

5th Serious liver injury leading to liver transplantation

The 5th reported case of serious liver injury leading to liver transplantation concerned a 54-year-old woman with no relevant medical history suggestive of underlying liver disorder, including no alcohol or drug abuse, did not travel; family history mentioned 2 sisters with unspecified hepatitis. The patient was started on Esmya as pre-operative treatment for a large myoma with urinary retention due to compression. Transaminase levels were normal before start of Esmya treatment and after 1 month of treatment. Increased levels of ALT (9.7xULN) and AST (5.7xULN) were reported 58 days after the first dose of Esmya and Esmya was discontinued. At 1 month following discontinuation of Esmya, transaminase levels continued to increase. At approximately 6 weeks after Esmya discontinuation, the patient reported nausea, vomiting and jaundice and was hospitalised. The patient was diagnosed with acute hepatitis, requiring liver transplantation at 59 days after last dose of Esmya.

The concomitant medication taken during Esmya treatment (flutrimazole cream, starting 7 days after first dose of Esmya) is not considered confounding. Following Esmya discontinuation, Depurpatic (vitamins, food supplement: black radish, desmodium, milk thistle, green anise and choline) was taken for 2 days, starting 2 days prior to hospitalisation. Reportedly, no other medications were taken in the period between Esmya discontinuation and hospitalisation.

Two or three days after hospitalisation (i.e., ~ 6 weeks after Esmya discontinuation), laboratory tests were performed. Autoimmune hepatitis was ruled out. Serology for viral hepatitis was as follows: cytomegalovirus (CMV) IgM and IgG positive, but negative for DNA-CMV, HAV (IgM neg, IgG pos), HBV (HBsAg neg, anti-HBc IgM neg), HEV (IgM neg), EBV (IgM neg, IgG pos), HIV neg. The role of CMV infection, either as de novo infection or reactivation, was not likely based on the absence of symptoms of CMV infection and no convincing evidence based on CMV serology and pathological findings in the explanted liver. Thus, acute hepatitis of viral aetiology was considered unlikely.

It was noted that the patient and the prescriber were compliant with the risk minimisation measures as per product information, however liver test values further deteriorated even when ulipristal acetate 5mg was discontinued and liver transplantation could not be prevented.

This case of serious liver injury suggests a causal association between ulipristal acetate and acute hepatitis leading to acute liver failure and liver transplantation with a high degree of certainty (probable/highly probable).

Other serious cases of liver injury reported between 1 March 2018 and 29 February 2020

Amongst the other 6 cases with serious liver disorder SMQ containing sufficient/partially sufficient information for causality assessment, the first 2 cases dated 2017, before liver monitoring was introduced as risk minimisation measures. However, as they were reported in 2018 after the finalisation of the Article 20 review of Esmya and the cut-off date of 28 February 2018, they were considered as part of this referral procedure.

The first case concerned a 48-49-year-old female who was treated for 81-82 days with Esmya (5 mg per day) for the indication uterine myomatosis, hypermenorrhoea and dysmenorrhoea. Symptoms of nausea and right upper quadrant abdominal pain were reported before treatment with Esmya was started. No liver function tests prior and during treatment are available. Although no specific dates and lab values were described, increased ALT, AST and GGT levels presumably after Esmya treatment were described. Liver lab values were normal about 2 months after first specified lab values were found and about 5 months after discontinuation of Esmya. Ultrasound results showed a homogenous normal sized liver. The patient had no history of hereditary liver disease, alcohol use, and viral infections and auto-immune hepatitis was excluded. Concomitant medications were Decristol, pravastatin, iodine and magnesium. The SmPC of pravastatin describes that serious liver injury cases are reported post-marketing. The causality of this case is difficult to assess, because laboratory values are missing, concomitant pravastatin use may have confounded the case and it cannot be excluded that liver damage was present before start of treatment with Esmya. However, it cannot be excluded that liver injury was caused by Esmya. Liver injury is therefore possibly related to treatment with Esmya.

The second case concerned a 43-year-old female who was treated with Esmya (5 mg per day) for about 8 months for the indication uterine fibroid. Liver test values were slightly increased (AST 1.5xULN and AST 1.2xULN). Acute hepatitis was diagnosed, but method of diagnosis was unknown. Two months later hepatic angioma was found with MRI, no liver laboratory values were reported, and Esmya was discontinued. About 1.5 months after discontinuation of Esmya, liver lab values were normal. No concomitant medication and no alcohol use were reported. Viral hepatitis and auto-immune hepatitis were excluded. Hepatic angioma was diagnosed after discontinuation of Esmya. Hepatic angioma could be an alternative cause for slightly increased liver test values. Based on the information provided (slightly increased lab values and unknown method of diagnosis of hepatitis), it is not clear whether this patient had a drug-induced liver disease. As the ALT/AST were below 2xULN, indicating that there are no signs of DILI. Therefore, this case seems to be unlikely related to Esmya.

The remaining 4 cases with serious liver disorder SMQ all occurred after finalisation of the Article 20 review of Esmya.

The third case concerned a 45-year-old female who was treated with Esmya (5 mg per day) for about 2 years for the indication uterine myoma and bleeding menstrual heavy. The patient discontinued Esmya because of increased liver lab values (ALT: 5.2xULN, AST 3.8xULN) presumably during treatment with the 6th treatment course of Esmya. The patient recovered about 2 months after discontinuation of Esmya. Reported concomitant medications were tranexamic acid and levothyroxine. Positive ANA test suggestive for autoimmune hepatitis; however, no steroid treatment started. The case lacks information on Hepatitis E test and alcohol use. In conclusion, a causal role for Esmya is possible, but with remaining uncertainty regarding viral or autoimmune hepatitis.

The fourth case concerned a 52-year-old female who was treated with Esmya (5 mg per day) for the indication excessive menstrual bleeding. Diagnosis of uterine myoma/fibroid was not reported. Viral hepatitis and auto-immune hepatitis were not excluded. Alcohol use was not reported. Not all alternative causes were therefore excluded. The patient started several other drugs and no indications and no discontinuations of these drugs are described, while some drugs are started more than once.

Since most exact start and stop dates of Esmya are not exactly known, it is not known whether Esmya was started before or after a concomitant drug was started. Hepatic adverse events are listed in the SmPC of the following concomitant treatments: rivaroxaban (rare to common), fluconazole (rare to common), etoricoxib (rare to common), amoxicillin (very rare), losartan (rare to unknown), hydroxyzine (unknown) and papaverine (not known). It is possible that the case is confounded by one or more of these concomitant drugs. It may be possible that liver values increased after start of Esmya and decreased after discontinuation of Esmya, but this is uncertain because of the unspecific start and stop dates of Esmya. It is therefore difficult to conclude that this case has a positive dechallenge and positive rechallenge for Esmya. The case is difficult to assess, because viral hepatitis, auto-immune hepatitis and alcohol use were not excluded as alternative causes, start and stop dates of Esmya are not exactly known, the case may be confounded by one or more concomitant drugs and positive dechallenge and positive rechallenge for Esmya are not certain. However, it cannot be excluded that liver injury was caused by Esmya. Liver injury is therefore possibly related to treatment with Esmya.

The fifth case concerned a 30-year-old female who was treated for 2 treatment courses of 3 months with Esmya (5 mg per day) for the indication uterine fibroid and menometrorrhagia. The patient had no history of alcohol intoxication/abuse. Liver values were normal during Esmya treatment. About 5 weeks after the last treatment of the second treatment course of Esmya the patient was diagnosed with paracetamolaemia. Paracetamol was discontinued. About 1.5 weeks later patient recovered following N-acetylcysteine treatment. Because of the diagnosis of paracetamolaemia, acute hepatitis was more likely caused by paracetamol treatment. The case is unlikely related to Esmya treatment.

The sixth case concerned a 34-year-old female who was treated with Esmya for the indication uterine myomatosis. The patient had three Esmya treatment courses of three months in the past. During the fourth treatment course with Esmya the patient was treated for 57 days with Esmya. Twenty-seven days after discontinuation of Esmya, the patient recovered. The patient used bio herbal infusion "La vie en herbe, les simples, framboisier" (rubus ideaus), in the last two years, which was not discontinued. The patient had no history of alcohol consumption. Viral hepatitis and auto-immune hepatitis were not excluded as alternative causes. However, because a positive dechallenge was reported, the increased liver lab values were possibly caused by Esmya.

Although there are remaining uncertainties due to missing data and possible confounders, a causal role for Esmya in 4 of these 6 cases reporting serious hepatic events is possible.

4.1.1.2. Effectiveness of the implemented risk minimisation measures

Following the completion of the Article 20 procedure in 2018, a set of risk minimisation measures was implemented for Esmya:

- the intermittent treatment of moderate to severe symptoms of uterine fibroids with Esmya was restricted to adult women of reproductive age not eligible for surgery. It was also clarified that Esmya could be used as one treatment course of pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. The PRAC also recommended that the initiation and supervision of treatment with Esmya should be restricted to physicians experienced in the diagnosis and treatment of uterine fibroids.
- Ulipristal acetate 5mg was contraindicated in patients with underlying hepatic disorders. In addition, it was recommended in the product information to perform liver function tests before starting each treatment course with Esmya, during treatment as well as two to four weeks after the discontinuation of treatment. Guidance on treatment initiation and discontinuation based on the results of these tests was included in the product information. Treatment was also recommended to be stopped in patients showing signs or symptoms compatible with liver injury

and to investigate the patient immediately. The adverse drug reaction of hepatic failure was also added to the product information with the frequency unknown.

- A patient card was also provided in each package of Esmya, to ensure that patients are adequately informed on the possible risks of liver injury and the implemented risk minimisation measures. In addition, the existing physician's guide to prescribing was updated accordingly.

To evaluate the effectiveness of monitoring of liver parameters in patients treated with Esmya and the adherence to the modified indication and to the contraindication of underlying hepatic disorder, the MAH of Esmya was requested to conduct a retrospective drug utilisation study through a chart review across not less of four major EU countries.

The study protocol for the drug utilisation study was agreed with PRAC in November 2019 with a plan to start the study in Q3 2020. However, the MAH of Esmya presented some findings from post-marketing spontaneous sources and from post-marketing solicited source to demonstrate effectiveness of the measures. In their review of the reported cases with Esmya after 1 August 2018 (announcement of EC decision on Article 20 procedure) 20 cases from EEA had ALT or AST > 3xULN (or > 90 IU/L) during Esmya treatment. From the analysis of these 20 cases, it can be concluded that the newly introduced risk minimisation measures were mostly followed in the clinical practice. In a limited number of cases, treatment discontinuation led to normalisation of the liver test results. However, in very rare cases liver test values further deteriorated even when Esmya was discontinued, where liver function monitoring could not prevent liver transplantation.

The MAH of Esmya also provided information from the PREMIUM study, a prospective, non-interventional, post-authorisation safety study (PASS) performed with Esmya (ulipristal acetate 5 mg) in the EU with the objective to evaluate the long-term safety of the endometrium. Overall, 1,532 patients were enrolled (including 1,319 patients in safety population with reported date of Esmya treatment start date) and based on the data available, no safety concerns regarding liver parameters were identified.

This study was however not designed to evaluate the risk of liver injury with ulipristal acetate 5mg nor the effectiveness of the risk minimisation measures in place to prevent that risk.

In addition, the PRAC noted that the 5th case of serious liver injury leading to liver transplantation described above occurred despite adherence by the patient and the prescriber to the implemented risk minimisation measures and that the liver test values had further deteriorated even when ulipristal acetate 5mg was discontinued. Liver transplantation could not be prevented in this case.

4.1.1.3. Conclusion on safety aspects

The risk of serious liver injury associated with ulipristal acetate was thoroughly reviewed in the previous Article 20 review which resulted in the restriction of both approved indications and implementation of several risk minimisation measures. In addition, the MAH of Esmya, Gedeon Richter, was requested to perform several studies including on the mechanism of ulipristal acetate associated liver injury. Moreover, `hepatic failure´ was adjudicated as an adverse drug reaction and drug induced liver injury (DILI) as an important identified risk for ulipristal acetate.

The non-clinical and pharmacology studies performed have not contributed to further knowledge regarding the mechanism of liver injury in association with ulipristal acetate. Based on the current knowledge, the hepatotoxicity associated with ulipristal acetate is considered to be of an idiosyncratic nature, making it difficult to identify susceptible patients who would be at an increased risk.

Where in the four previously reported cases of serious liver injury leading to liver transplantation (reviewed in the context of the 2018 Article 20 review) some remaining uncertainty regarding the role

of ulipristal acetate in the development of liver injury was identified, the recently reported case of serious liver injury (5th cumulative case) suggests a causal association between ulipristal acetate and acute hepatitis leading to acute liver failure and liver transplantation with a considerably higher degree of certainty (probably/highly probable).

The risk minimisation measures implemented following the Article 20 review were intended to identify and exclude patients with underlying liver disorders, to ensure monitoring of patients for liver enzymes before, during and after the first two treatment courses of Esmya and to recommend treatment discontinuation in case of ALT/AST levels >3xULN. However, the 5th case of serious liver injury leading to liver transplantation, occurring despite adherence to the agreed risk minimisation measures, confirms that the current recommendations in place for liver monitoring as included in the SmPC may not prevent serious liver injury leading to liver transplantation in all patients.

4.1.2. Efficacy aspects

The efficacy of ulipristal acetate 5mg in the treatment of symptoms of uterine fibroids has been demonstrated at the time of the initial marketing authorisation of Esmya and no new data regarding efficacy have been submitted by the MAHs within this referral procedure.

4.1.2.1. Pre-operative treatment of moderate to severe symptoms of uterine fibroids

The efficacy of fixed doses of ulipristal acetate 5 mg and 10 mg once daily was evaluated in two Phase 3 randomised, double-blind, 13 week studies recruiting patients with very heavy menstrual bleeding associated with uterine fibroids.

Study 1 was double-blind placebo controlled. Patients in this study were required to be anaemic at Study entry (Hb < 10.2 g/dl) and all patients were to receive oral iron 80 mg Fe++ in addition to study medicinal product. Study 2 contained the active comparator, leuprorelin 3.75 mg given once per month by intramuscular injection. In Study 2, a double-dummy method was used to maintain the blind. In both studies menstrual blood loss was assessed using the Pictorial Bleeding Assessment Chart (PBAC). A PBAC >100 within the first 8 days of menses is considered to represent excessive menstrual blood loss.

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

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

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

In study 1, a statistically significant difference was observed in reduction in menstrual blood loss in favour of the patients treated with ulipristal acetate compared to placebo (see Table 1 below), resulting in faster and more efficient correction of anaemia than iron alone. Likewise, patients treated with ulipristal acetate had a greater reduction in myoma size, as assessed by MRI.

In study 2, the reduction in menstrual blood loss was comparable for the patients treated with ulipristal acetate and the gonadotrophin releasing hormone-agonist (leuprorelin). Most patients treated with ulipristal acetate stopped bleeding within the first week of treatment (amenorrhoea).

4.1.2.2. Intermittent treatment of moderate to severe symptoms of uterine fibroids

The efficacy of repeated treatment courses fixed doses of ulipristal acetate 5 mg or 10 mg once daily was evaluated in two Phase 3 studies assessing up to 4 intermittent 3-month treatment courses in patients with heavy menstrual bleeding associated with uterine fibroids.

Study 3 was on open-label study assessing ulipristal acetate 10 mg, where each of the 3-month treatment was followed by 10 days of double-blind treatment with progestin or placebo. Study 4 was a randomised, double-blind clinical study assessing ulipristal acetate 5 or 10 mg.

Studies 3 and 4 showed efficacy in controlling uterine fibroid symptoms (e.g. uterine bleeding) and reducing fibroid size after 2 and 4 courses.

In study 3, treatment efficacy has been shown over >18 months of repeated intermittent treatment (4 courses of 10 mg once daily), 89.7% of patients were in amenorrhoea at the end of the treatment course 4.

In study 4, 61.9% and 72.7% of patients were in amenorrhoea at the end of both treatment course 1 and 2 combined (5 mg dose and 10 mg dose, respectively, p=0.032); 48.7 % and 60.5 % were in amenorrhoea at the end of all four treatment courses combined (5 mg dose and 10 mg dose,

respectively, p=0.027). At the end of treatment course 4, 158 (69.6%) subjects and 164 (74.5%) subjects were assessed as being in amenorrhoea, in the 5 mg dose and 10 mg dose respectively (p=0.290).

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

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

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

[b] Patients with missing values were exluded from the analysis.

[c] N and % include withdrawn patients

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

In all Phase III studies including repeated intermittent treatment studies, a total of 7 cases of hyperplasia were observed out of 789 patients with adequate biopsies (0.89%). The vast majority spontaneously reversed to normal endometrium after resumption of menstruation during the off-treatment period. The incidence of hyperplasia did not increase with repeated treatment courses, including data on 340 women who received up to 4 courses of ulipristal acetate 5 or 10 mg and limited data of 43 women who received up to 8 courses of ulipristal acetate 10 mg. The observed frequency is in line with control groups and prevalence reported in literature for symptomatic pre-menopausal women of this age group (mean of 40 years).

4.1.2.3. Conclusion on efficacy aspects

Efficacy pre-operative treatment

At the end of one treatment course (3 months), 73.4% and 75.3%, respectively, of patients in two different phase III studies reported amenorrhoea and the median fibroid volume had been reduced compared to baseline by 21.2% and 35.6%, respectively. The reduction in myoma size, which may facilitate surgery, as well as reduction in blood loss and anaemia, which will improve the general health of the patient, are clinically relevant. However, the clinical benefits of the pre-operative treatment could be considered limited as it is restricted to one treatment course prior to surgery, and there are other short-term treatment alternatives.

Intermittent treatment of moderate to severe symptoms of uterine fibroids

At the end of the fourth treatment course, corresponding to one year of treatment, 69.6% of patients reported amenorrhoea and the median reduction of myoma volume from baseline was 71.8% in one phase III study. The benefits of ulipristal acetate are considered largest in the intermittent treatment indication, i.e. for patients who are not eligible for surgery, since for those patients there are next to no other obvious treatment alternatives. Those who are not eligible for surgery may include women who, for various reasons, constitute a surgical risk, such as being obese, suffering from concurrent

disease, being treated with certain medications or wanting to preserve fertility. Thus, ulipristal acetate 5mg may provide clinically relevant benefits to women who are not eligible for surgery, whose health and quality of life are affected by symptoms of uterine fibroids, in particular heavy bleeding.

5. Expert consultation

Upon request from the PRAC, an ad-hoc expert group meeting was convened on 2 July 2020.

Asked about the impact in clinical practice of the removal of the pre-operative treatment for ulipristal acetate, most experts agreed that alternatives exist that provide a sufficient efficacy profile in this indication in the pre-operative stage, such as GnRH analogues. Some experts pointed out that the reduction of volume of fibroids by ulipristal acetate is not considered very high and thus ulipristal acetate in the pre-operative setting does not profoundly impact the success of surgery. It was however highlighted that ulipristal acetate could still be an additional option for those women who would like to opt for this treatment in view of having a chance of reducing the fibroid volume to the point of having hysteroscopic myomectomy in the long term and with the aim to preserve fertility – if that proves feasible.

The experts agreed that when considering ulipristal acetate as an intermittent treatment it is very important to look at risks of the alternative option that is surgery. The mortality rate after hysterectomy range from 1 in 500 to 1 in 3000; while major complications such as bleeding, intestinal perforation are at the frequency of 1 in 100. In this context of a relative risk assessment among treatment options, most experts stressed the need of having ulipristal acetate as a treatment option in this indication. One expert stressed that their clinic treats almost all patients surgically (>99%) – however the majority were perimenopausal - and that ulipristal acetate 5mg has not been in use since the recommendations were issued after the latest referral. It was indicated that having more pharmacogenomics data would be desirable to profile patients for the risk of liver injury before starting them on UPA as intermittent treatment. Surgery may not be suitable for several reasons – such as in the case of obese patients, patients at risk of venous thrombosis, patients who have tried other treatments which failed, and it is also important to consider the patient population that does not want to undergo surgery, such as younger patients who would like to preserve fertility.

From a patient perspective, it was stressed the importance of choice and informed decision of the individual taking into account all available options.

Overall, the experts agreed that ulipristal acetate should remain a treatment option but emphasised the importance of a detailed analysis of the risks and careful review of the individual case before any decision on the treatment is made.

The experts were asked to discuss the feasibility in clinical practice of defining a patient population that is not eligible for hysterectomy or surgery and for which ulipristal acetate would be the only treatment option of moderate to severe symptoms of uterine fibrosis, and how such selection of patients would be done in clinical practice.

The experts considered counselling of patients to be the centre of decision-making: patients need to be made aware of the risks and benefits of both surgery and ulipristal acetate treatment. It was highlighted that patients that are not eligible for surgery are patients that do not want to undergo surgery (for whatever reason) or are at higher risk of complications when they undergo surgery (e.g. because of surgical history or BMI etc), and that hardly any patients have an absolute contraindication to undergo surgery.

The experts recognised that data on the benefits of ulipristal acetate 5mg beyond symptom relief, i.e. avoiding surgery/hysterectomy in the longer term are currently lacking, the need for randomised

clinical trials and long term follow up of cohorts has been emphasised. It was noted that with a good selection (age, symptoms, number and size of myomas) of patients, surgery could be avoided in a high percentage of patients. It was highlighted that real-world data about this point could be obtained from the PREMYA study, a long-term follow-up cohort study, to help answer this question.

Although no randomised trials have been conducted to demonstrate the benefit of ulipristal acetate 5mg as a pre-treatment before hysteroscopic myomectomy, some experts had good experience in this perspective, and said it might be a good trial objective for the future. In view of hysterectomy and abdominal myomectomy, an alternative has either proven to be superior or is very likely to be superior (GnRH analogues). It was also highlighted that sometimes a pre-treatment works so well that the patients decide to cancel surgery.

When asked about the risks associated with ulipristal acetate 5 mg as compared to the risks associated with hysterectomy/surgery procedure and how could these be best communicated to the patient, the group stressed the importance to balance all available options in each individual situation. For this purpose, the experts strongly recommended that the benefits and risks of ulipristal acetate should be sufficiently communicated – most importantly the risk of liver injury – and placed in the context of the benefits and risks of all other available options, as outlined above. This information should be evidence-based and preferably given to the patient as written material to facilitate open discussion between the healthcare professionals and the patients in order to make informed decisions on the best treatment.

6. Benefit-risk balance

The efficacy of ulipristal acetate 5mg in the treatment of symptoms of uterine fibroids has been demonstrated at the time of the initial marketing authorisation of Esmya. The clinical benefits of the pre-operative treatment could be considered limited as it is restricted to one treatment course prior to surgery, and there are other short-term treatment alternatives. The benefits of ulipristal acetate are considered largest in the intermittent treatment indication, i.e., for patients who are not eligible for surgery, since for those patients, treatment alternatives are limited. Those who are not eligible for surgery may include women who, for various reasons, constitute a surgical risk, such as being obese, suffering from concurrent disease, being treated with certain medications or wanting to preserve fertility. Thus, ulipristal acetate 5mg may provide clinically relevant benefits to women who are not eligible for surgery, whose health and quality of life are affected by symptoms of uterine fibroids, in particular heavy bleeding.

The risk of drug induced liver injury (DILI) in association with use of ulipristal acetate 5mg has been reviewed thoroughly in the previous Article 20 review of Esmya. As outcome of this review, `hepatic failure´ was adjudicated as an adverse drug reaction and DILI as an important identified risk for ulipristal acetate, both approved indications were restricted, and several risk minimisation measures were implemented. In addition, the MAH of Esmya was requested to perform several studies including on the mechanism of ulipristal acetate associated liver injury to further characterise this risk. However these studies have not contributed to further elucidate the mechanism of liver injury in association with ulipristal acetate 5mg and based on the available evidence, the hepatotoxicity associated with ulipristal acetate is considered to be of an idiosyncratic nature, making it difficult to identify susceptible patients who would be at an increased risk.

Since the previous review, Gedeon Richter noted that the patient exposure to Esmya had registered a significant decrease (over 50%). Between 1 March 2018 and 29 February 2020, 476 new cases were received within the hepatic disorder SMQ (serious and non-serious events); of those, 97 cases were serious with 7 cases containing sufficient/partially sufficient information for causality assessment,

including one case of serious liver injury leading to liver transplantation (5th cumulative case). For this case, no confounding factors were identified, and other plausible aetiologies were ruled out; consequently, causality between ulipristal acetate and acute hepatitis leading to acute liver failure and liver transplantation was assessed as probable/highly probable, i.e. with a considerably higher degree of certainty.

It was also noted that a progression in the development of hepatic failure leading to liver transplantation could not be prevented. This case therefore confirms that the recommendations for liver monitoring as included in the product information further to the previous referral were not able to prevent serious liver injury leading to liver transplantation in all patients.

In the context of this review, the MAHs were asked to discuss the need and feasibility for any further risk minimisation measures to further mitigate the risk of serious liver toxicity, including changes to the product information, as well as proposals to monitor their effectiveness.

To further minimise the risk, the MAH of the originator product Esmya has proposed to withdraw the indication for pre-operative treatment, indicating that, the pre-operative treatment could be replaced by the use of a GnRH agonist for short-term use. As pointed out by some experts consulted in the context of this review, the reduction of volume of fibroids by ulipristal acetate 5mg is not considered very high and thus the use of this product in the pre-operative setting does not profoundly impact the success of surgery. It was also noted by most experts that alternatives exist for this indication in the pre-operative stage. In view of the above and taking into account the risk of serious liver injury leading to liver transplantation with ulipristal acetate 5mg, the benefit-risk balance of ulipristal acetate 5mg in the pre-operative treatment of moderate to severe symptoms of uterine fibroids is considered unfavourable for this indication and this indication should therefore be removed.

To further minimise the risk, the MAH of Esmya also proposed a restriction of the target population for the intermittent indication to patients *not eligible for hysterectomy.* However, concerns were raised on the definition of this subset of patients. From the discussions in the expert group convened in the context of this review, it became apparent that the proposed description/definition of this subset of patients appears very broad (e.g., women with apparent medical contraindications for surgery, women having failed other treatment options, women wanting to preserve fertility, and women not willing to undergo surgery). Depending on the interpretation in clinical practice of "patients not willing to undergo surgery" or "patients not suitable for surgery/hysterectomy", this indication may apply to many patients thus rendering the restriction of the indication to "not eligible to surgery/ hysterectomy" weak as a risk minimisation measure. The experts also recognised that data on the benefits of ulipristal acetate 5mg beyond symptom relief, i.e., avoiding surgery/hysterectomy in the longer term are currently lacking.

The experts consulted during the review recommended that the benefits and risks of ulipristal acetate should be sufficiently communicated to the patients – most importantly the risk of liver injury – and stressed the importance of placing those benefits and risks in the context of the benefits and risks of all other available options. The PRAC took the reflections from the experts that surgical treatment alternatives to treat moderate to severe symptoms of uterine fibroids are not without risk. However, PRAC considered that making a fair comparison between surgical and pharmacological treatments was challenging as it would have to include different kinds of short- and long-term outcomes on health by either treatment, preferably based on comparative studies. Surgical treatment can lead to immediate cure but may convey, in rare cases, a risk of short- or long-term sequelae, whereas pharmacological treatments mainly result in alleviation of symptoms but, in rare instances, may lead to serious adverse events. Gedeon Richter, the MAH of Esmya, also acknowledged that the feasibility of ensuring that all patients have equal opportunity to make an adequately informed decision, including appropriate information sharing by the treating physician regarding the risks of treatment options and its relevant

consequences, should be considered, and that based on the available tools and communication channels, significant limitations could be identified.

PRAC was of the view that the proposed changes to the indications (i.e., removal of the preoperative indication and restriction of the intermittent indication to *not eligible to surgery/hysterectomy*) may further reduce the number of patients exposed to ulipristal acetate 5mg. However, as acknowledged by the MAH of Esmya, the patient group for whom the therapy is suitable cannot be scientifically well defined, which would make the decision of treatment with ulipristal acetate 5mg rather subjective. In addition, in view of the idiosyncratic nature of the risk and the difficulty to predict its occurrence (e.g., by identifying relevant risk factors), the PRAC considered that the risk of severe liver injury would not be sufficiently reduced in those who would still be exposed. The experts consulted also could not identify a population where the risk could be predicted and therefore prevented. PRAC also noted the feasibility limitations of ensuring adequate information is made available to all patients for an informed decision and was of the view that no further risk minimisation measures could be implemented that would prevent the risk of severe liver injury. In view of the above, PRAC concluded that the benefit-risk balance of ulipristal acetate 5mg was unfavourable as intermittent treatment of moderate to severe symptoms of uterine fibroids.

In view of the seriousness and idiosyncratic nature of the risk of serious liver injury, the occurrence of hepatic failure despite the implemented risk minimisation measures, that neither further risk measures to prevent and reduce the risk was identified nor a sub-population where the benefit risk balance of ulipristal 5mg could be positive, the PRAC concluded that this risk outweighs the benefits of ulipristal acetate 5mg in all its indications. As no condition, if fulfilled in the future, would demonstrate a positive benefit-risk balance for these products, the PRAC recommended the revocation of the marketing authorisations for ulipristal acetate 5mg medicinal products.

7. Grounds for the recommendation

Whereas

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC resulting from the evaluation of data from pharmacovigilance activities, for ulipristal acetate 5mg medicinal products;
- The PRAC reviewed the information available to the Committee on ulipristal acetate 5mg and the risk of serious liver injury, including the data provided by the marketing authorisation holders of ulipristal acetate 5mg in writing and in oral explanations and the outcome of the consultation with the ad-hoc expert group convened in the context of this procedure;
- The PRAC reviewed all cases of serious liver injury reported among women treated with ulipristal acetate 5 mg for the treatment of symptoms of uterine fibroids, including a new case of serious liver injury leading to liver transplantation (the 5th case cumulatively) reported although the risk minimisation measures agreed as outcome of the previous Article 20 referral were followed. The PRAC concluded that the causal association of ulipristal acetate 5mg with serious liver injury was probable/highly probable and noted that a progression in the development of hepatic failure leading to liver transplantation could not be prevented;
- The PRAC discussed further risk minimisation proposals and could not identify any additional measures that would ensure effective minimisation of the risk to an acceptable level. In view of the seriousness and idiosyncratic nature of the risk, the PRAC concluded that this risk outweighs the benefits of ulipristal acetate 5mg in the treatment of the symptoms of uterine fibroids. No sub-

group of patients in which the benefits of ulipristal acetate 5mg would outweigh the risks could be identified;

- Furthermore, the PRAC could not identify any condition, the fulfilment of which would demonstrate a positive benefit-risk balance of ulipristal acetate 5mg medicinal products.

The Committee, as a consequence, considers that the benefit-risk balance of ulipristal acetate 5mg medicinal products for the treatment of symptoms of uterine fibroids is not favourable and recommends, pursuant to Article 116 of Directive 2001/83/EC, the revocation of the marketing authorisations of all ulipristal acetate 5mg medicinal products.

Divergent positions to the PRAC recommendation

Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure No: EMEA/H/A-31/1496

Esmya EMEA/H/A-31/1496/C/2041/0049

Ulipristal Acetate Gedeon Richter EMEA/H/A-31/1496/C/5017/0002

Ulipristal acetate 5mg

Divergent statement

The following PRAC Member(s) consider(s) that the benefit risk ratio of ulipristal acetate 5mg remains favourable in a restricted indication, based on the following grounds:

- While it has been concluded that the 5th case of serious liver injury has a probable causal relationship with Esmya, the reporting rate of serious liver injury of 0.52/100,000 prior to the previous Article 20 procedure and 0.51/100,000 since the Article 20 procedure is in line with the most conservative background incidence of death/liver transplantation of 0.55 cases per 100,000 inhabitants of Catalonia (Ibañez 2002). However, in view of the new case with probable causality despite adherence to risk minimisation measures, existing measures should be strengthened.

- The benefits of ulipristal acetate 5mg in the intermittent indication are considered relevant for a subgroup of women with moderate to severe symptoms of uterine fibroids, i.e., for patients who are not eligible for surgery, since for those patients there are next to no other obvious treatment alternatives. Those who are not eligible for surgery may include women who, for various reasons, constitute a surgical risk, such as being obese, an increased risk of venous thrombosis, suffering from concurrent disease, being treated with certain medications or wanting to preserve fertility. Thus, ulipristal acetate 5mg may provide clinically relevant benefits to women who are not eligible for surgery, whose health and quality of life are affected by symptoms of uterine fibroids, in particular heavy bleeding. At the end of the fourth treatment course, corresponding to approximately two years of treatment (4 courses of 3 months with re-treatment courses starting in the first week of the second menstruation following the previous treatment course completion), 69.6% of patients reported amenorrhoea and the median reduction of myoma volume from baseline was 71.8% in one phase III study.

- An important aspect to consider is that other surgical options have their own risks, including adverse effects on fertility. The experts consulted during an ad hoc expert group meeting agreed that when considering ulipristal acetate 5mg as an intermittent treatment it is very important to look at the risks related to the alternative options. Hysterectomy is associated with major complications such as bleeding, intestinal perforation (incidence 1 in 100), but also with fatal outcomes (ranging from 1 in 500 to 1 in 3,000), so all with a higher incidence than the reporting rate of serious liver injury with Esmya. Also, less invasive alternative surgical treatments available have their risks, which also need to be taken into account in the decision whether or not to operate. Abdominal myomectomy confers substantial risks with respect to fertility, risks of

intraoperative conversion to hysterectomy, and frequent development of postoperative intra-uterine adhesions. Recurrence of fibroids is also common and additional treatment after myomectomy may be required.

- The expert group indicated that it is also important to consider the patient population that does not want to undergo surgery, such as younger patients who would like to preserve fertility.

- Overall, the small risk of serious liver injury is outweighed by the benefits of ulipristal 5mg in the intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women who have not reached menopause when uterine fibroid embolisation and surgical treatment options are not suitable or have failed. Furthermore, the risk of serious liver injury should be adequately described in the product information and educational materials.

- As also stressed by the ad hoc expert group, it is important that the individual situation is carefully reviewed and risks are considered before any decision on the treatment is made. Counselling of patients is key for decision making. This will be facilitated by revised product information and educational materials, informing HCPs and patients about the risk of serious liver injury.

- The indication of one treatment course of pre-operative treatment is considered of less benefit as it reflects a situation when surgery is planned as an alternative medical option is available for short-term pre-operative use (i.e., a GnRH agonist). Therefore, the proposal to remove the pre-operative treatment with ulipristal acetate 5mg proposed by the MAH is endorsed as additional measure to further restrict the population at risk.

PRAC Members expressing a divergent opinion:

- Jan Neuhauser
- Nikica Mirošević Skvrce
- Eva Jirsová
- Kirsti Villikka
- Zane Neikena
- John Joseph Borg
- Menno van der Elst
- Roxana Stefania Stroe
- Michal Radik
- Eva A. Segovia
- Birgitta Grundmark
- Milou-Daniel Drici
- Hedvig Marie Egeland Nordeng
- Raymond Anderson