

Annex II
Scientific conclusions

Scientific conclusions

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 subgroup 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 adequately 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 with a conservative background incidence of death/liver transplantation of 0.55 cases per 100,000 inhabitants as described by Ibáñez in 2002¹.

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 amenorrhea 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 Multicèntric 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 amenorrhea 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 embolization are similar to those after surgery, but embolization 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 available 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.