Annex IV

Scientific conclusions

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Three cases of serious liver injury leading to a hepatic transplantation were reported between the marketing authorisation of Esmya (ulipristal acetate) and November 2017. In addition, other cases of hepatic injury were also reported post marketing for Esmya. Given the estimated exposure to Esmya of approximately 200,000 to 275,000 patient-years, the number of cases of serious liver injury leading to liver transplantation appears higher than expected, although background incidence on drug induced liver injury is uncertain. No information on hepatic events was at that time included in the Product Information of Esmya. Acknowledging the uncertainty regarding background incidence and the information in the reported cases, the seriousness of the reported cases raises concern. Since a possible causal relationship between Esmya and acute liver failure could not be ruled out, these cases prompted an in-depth investigation of this risk and its impact on the benefit risk balance of Esmya.

On 30 November 2017, the European Commission triggered a procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data, and requested the PRAC to assess the impact of the above concerns on the benefit-risk balance of Esmya and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

Overall summary of the scientific evaluation by the PRAC

Esmya (ulipristal acetate, 5 mg) is a centrally authorised medicinal product indicated for pre-operative treatment, as well as intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

PRAC considered all the data submitted by the MAH, as well as data provided by the National Competent Authorities including follow-up information on cases of liver transplantation. The views expressed by *ad-hoc* experts consulted during the course of the procedure were also considered.

Uterine fibroids are the most common female pelvic tumour. Although uterine fibroids are benign, moderate to severe forms are often associated with significant morbidity, such as heavy bleeding, anaemia, pain, discomfort and reduced quality of life. As assessed in the initial marketing authorisation of Esmya, the clinical efficacy of ulipristal acetate in the pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age was based on short-term studies demonstrating the ability of the active substance to reduce fibroid-related bleeding, anaemia and fibroid size if administered in a daily dose of 5 mg for up to three months. The marketing authorisation of Esmya was extended to include the therapeutic indication for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. This last indication was authorised based on results from another study providing data for up to 4 intermittent treatment courses of 3 months each with ulipristal acetate along with data for repeated treatment courses from the previous studies. Through a pronounced reduction of bleeding, reducing anaemia and related symptoms, Esmya has been demonstrated to rapidly contribute to the improvement of the quality of life in patients who did not undertake a surgical treatment. Of note, menopause constitutes a natural end to the need for treatment.

It was noted that no signal of hepatic toxicity was identified from non-clinical or clinical studies on Esmya. However, due to exclusion criteria covering patients with elevated transaminases, or other signs of liver disease, as well as the limited size of the safety database in these studies, the absence of findings in clinical trials has to be interpreted with caution. Also, due to hormonal differences between rodents and humans, the toxicological liver safety findings obtained in rodents were assessed as less relevant for humans. In post marketing settings, all of the reported cases lack information hampering causality assessment, and causal relationship with Esmya and serious hepatic injury is therefore not

firmly established. However, there is sufficient information from these cases to conclude that there is at least a reasonable possibility that Esmya may infrequently contribute to hepatic injury.

Based on the safety findings and possible mechanism of action, the experts of the ad hoc experts group were of the view that a causal association between Esmya and severe liver injury is plausible. In particular, there was a consensus among hepatologists that in at least 2 cases reported, a relation with the use of Esmya could be observed.

Although the general characteristics of Esmya do not support it to be a typical DILI causing agent, based on the current review, and taking experts views into consideration, the PRAC concluded that Esmya (ulipristal acetate) may carry a risk for serious liver injury. The available data raise serious concerns, and warrant risk minimisation measures to be taken.

Uterine fibroids are the single most common indication for hysterectomy[1]. Hysterectomy is a very common curative surgical procedure within gynaecology associated with a low mortality (mortality figures quoted range from 0.02% to 0.17%) and a low risk of intra- or postoperative complications (quoted from 5% to 8%). Other surgical treatments such as myomectomy and uterine artery embolisation are also valid alternatives to hysterectomy, but they are not suitable for all cases and are also associated with a higher rate for complications than hysterectomy. However, it is recognised that a surgical treatment is not suitable for all women, due to their medical history, co-morbidities or willingness to preserve fertility.

In view of the existing concerns on recently reported cases of serious liver injury and acknowledging that the magnitude of the benefit differs for different clinical situations, the PRAC considered that the use of Esmya should be limited. Taking into account the clinical utility of Esmya in the intermittent treatment indication, where no other long-term pharmacological alternative is authorised, this indication should be limited to adult women of reproductive age who are not eligible for surgery.

The pre-operative treatment may be considered of least benefit as it reflects a situation when surgery is planned; however reductions in myoma size as well as reductions in blood loss and anaemia are considered of clinical significance. PRAC considered that it should be clarified in in the wording of the indication that in line with the current posology Esmya is to be used for a single treatment course in pre-operative setting.

Taking into account the experts' views on the topic, and after a thorough review of the available data, PRAC considered that the following risk minimisation measures should be recommended.

In order to exclude patients that would be potentially more susceptible to hepatic insult from the treatment with Esmya, the product should be contraindicated in patients with underlying hepatic disorder. In addition, the PRAC considers that warnings regarding monitoring and stopping criteria should be implemented, in order to identify a hepatic injury of any origin before the patient experiences symptoms, which could reduce the risk of developing serious injury.

Therefore, liver function tests should be performed before starting treatment with Esmya, monthly during the first two courses of treatment as well as two to four weeks after the discontinuation of the treatment. In line with the exclusion criteria in the clinical studies of Esmya, patients with ALT or AST> 2 x ULN (isolated or in combination with bilirubin >2 x ULN) should not initiate treatment. In addition, patients who develop transaminase levels (ALT or AST) > 3 x ULN during treatment should stop treatment and be closely monitored. Usually, DILI events occur within the first 6 months after starting a new medication[2]. Based on the reported post-marketing cases of potential liver injury with Esmya,

[1] Stewards EA; Uterine Fibroids. Lancet, 27 January 2001; 357(9252):293-8.
[2] Chalasani NP, Hayashi PH, Bonkovsky HL et al. ACG Clinical Guideline: The diagnosis and management of idiosyncratic drug-induced liver injury. The American Journal of Gastroenterology. July 2014; 109(7):950-66.

and assuming that all such cases are due to Esmya, regardless of causality, the peak time to onset of liver injury is around 140 days and the vast majority of the reported potential drug induced liver injuries occurring between 1 and 8 months (2 treatment cycles including 2 months pause). This is the rationale that justifies the mandatory liver monitoring within the first 2 treatment courses, while during later courses, monitoring is recommended as clinically indicated. Of note, the development of drug induced liver injury generally tends to be a gradual phenomenon, developing over 1-4 weeks. More frequent monitoring than monthly is not considered practically feasible. The PRAC considers it appropriate to also monitor liver function 2 to 4 weeks after the treatment has stopped, since for some of the reported cases, liver injury was reported a few weeks after the discontinuation of the treatment.

In order to ensure that decisions on the initiation and continuation of the treatment are made by physicians who are familiar with diagnosis of uterine fibrosis, the PRAC also recommends that the initiation and supervision of treatment with Esmya should be restricted to physicians experienced in the diagnosis and treatment of uterine fibroids.

The existing educational material (physician's guide) should also be updated with these recommendations, and the issuing of a Direct Healthcare Professional Communication (DHPC) is also considered appropriate, to inform healthcare professionals of the recommendations of the present review. In order to ensure that patients are adequately informed on the possible risks of liver injury and the implemented risk minimisation measures, a patient card should be issued. Patients should be informed of potential adverse reactions related to liver that could be caused by the use of Esmya, as well as on the need to warn their physicians on any liver problems they may have. Patients should inform physicians on any liver problems they may have, and be also aware of the liver function monitoring tests to be performed before the treatment, during the treatment and after its discontinuation.

The PRAC was also of the view that the reported cases of liver injury should be closely monitored; to this effect a targeted follow up questionnaire has been included in a revised risk management plan (RMP). The MAH should implement these questionnaires and their results should be discussed in future periodic safety update reports (PSURs).

In the view of the remaining uncertainties, the PRAC is of the view that further data on Esmya and liver injury should be collected. The PRAC considers that in vitro studies should be performed by the MAH, in order to better characterize the mechanistic profile of DILI as associated with Esmya. In addition, in order to analyse data on risk of liver injury related with Esmya and on effectiveness of risk minimisation measures, observational studies should be performed.

In conclusion, the PRAC considered that the benefit-risk balance of Esmya remained favourable subject to the amendments of the terms of the marketing authorisations. The temporary measure recommended by the PRAC in February 2018, to not treat any new patients is superseded by these new recommendations.

Grounds for PRAC recommendation

Whereas,

- The PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data for Esmya (ulipristal acetate).
- The PRAC reviewed the totality of the data regarding the risk for liver injury with Esmya provided by the marketing authorisation holder and National Competent Authorities on cases of liver injury and liver transplantation reported since the initial marketing authorisation of the product. Data from clinical trials, non-clinical studies including in vitro testing were also

reviewed. The PRAC also considered the views expressed by experts at an ad hoc expert group meeting.

- The PRAC concluded that Esmya (ulipristal acetate) may carry a risk for serious liver injury. While uncertainties around causality remain, PRAC recognised the very serious outcome of the reported cases of liver injury. Balancing this to the benefits of Esmya treatment of moderate to severe symptoms of uterine fibroids, the PRAC concluded that the indicated population should be restricted for safety reasons. Furthermore, measures to minimise a risk for liver injury should be implemented.
- The PRAC recommended that intermittent treatment of moderate to severe symptoms of uterine fibroids with Esmya should be restricted to adult women of reproductive age who are not eligible for surgery. It is also clarified that Esmya can 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.
- The PRAC further concluded that Esmya should be contraindicated in patients with underlying hepatic disorder. In addition, the PRAC recommended the performance of 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 are included in the product information. Treatment should be stopped in patients showing signs or symptoms compatible with liver injury and the patient should be investigated immediately.
- The PRAC also found it necessary to introduce a patient card to be 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 should be updated accordingly.
- The PRAC was also of the opinion that mechanistic studies should be conducted, to further investigate a possible mechanism for hepatic toxicity. In addition, observational studies should be performed to further characterise the hepatic risk and to evaluate the effectiveness of implemented risk minimisation measures.

In view of the above, the Committee considers that the benefit-risk balance of Esmya (ulipristal acetate) remains favourable subject to the agreed amendments to the product information and the additional risk minimisation measures. The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for Esmya (ulipristal acetate).

CHMP opinion

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.