Annex IV

Scientific conclusions

Scientific conclusions

Four cases of serious liver injury leading to a hepatic transplantation were reported since the marketing authorisation of Esmya. In addition, several other cases of hepatic impairment associated with the use of the product were reported. Given the estimated exposure to Esmya of approximately 175,000 patient years, the number of cases of subacute severe liver impairment leading to liver transplantation with Esmya appears higher than expected, although background incidence on drug induced liver injury is uncertain. No information on hepatic events is currently 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. Three out of those four cases of serious liver injury were reported to the competent authorities before November 2017. The possible causal relationship between Esmya and acute liver failure of those three cases prompted an in-depth investigation of this risk and its impact on the benefit risk balance of Esmya is warranted.

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.

A fourth case of hepatic liver failure leading to transplantation was reported on 30th of January 2018. Taking into account this new case and the totality of the reported cases, a preliminary review and assessment of all the data available was performed by PRAC, to consider if provisional measures were needed while the issue is being furtherly reviewed. The preliminary review was concluded on 8th of February 2018. The current recommendation relates only to provisional measures recommended by the PRAC for Esmya based on the preliminary data available at this time. These provisional measures are without prejudice to the outcome of the ongoing review under Article 20 procedure.

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.

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 therapeutic indication for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age was 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. In patients suffering from heavy menstrual bleeding associated with uterine fibroids, repeated 3-month treatment courses with ulipristal acetate provide a medical alternative to surgery and have the potential to reduce the need for surgical intervention.

PRAC reviewed all data currently available from post-marketing settings and from clinical trials as well as the responses provided by the marketing authorisation holder on cases of serious liver injury reported with Esmya. In addition to these, a preliminary assessment of a recently reported case of liver transplantation with fatal outcome was performed. Follow-up information on this case was also reviewed by the PRAC, as well as additional information provided by the Marketing Authorisation Holder while the review was ongoing.

No signal of hepatic toxicity was identified during the review of non-clinical or clinical trials of Esmya inducing hepatic toxicity. The absence of findings in clinical trials has to be interpreted with caution as abnormal values of ALT/AST was an exclusion criterion *as per* protocols

In post-marketing settings, a total of four cases of acute liver failure leading to liver transplantation including one with fatal outcome have been reported in patients exposed to Esmya. In addition, several cases of hepatic injury in patients using Esmya were reported. The impact of the new safety findings in the currently authorised indications of Esmya cannot be evaluated with certainty at present in view of the limited data available. An in depth assessment is needed to firmly establish factors that may have caused the reported serious hepatic injuries. It is therefore too early to conclude that the risk of hepatotoxicity is associated with the use of Esmya for all cases. However, there are a few cases of serious hepatic injury, where no other obvious explanation has been identified, despite uncertainty in relation to possible confounding. Among those, there are positive de-challenge cases. In addition, PRAC considers that involvement of Esmya in at least two of the four transplantation cases reported and in two additional less serious cases, is at least plausible. Nevertheless, the review of cumulatively reported post-marketing cases does not allow a firm conclusion at this stage. Even though it is unclear at this stage whether monitoring of transaminases would necessarily prevent further severe cases, liver function monitoring is expected to be an important measure to detect liver injury during treatment, and likely reduce the incidence of severe cases.

Given the estimated exposure to Esmya of approximately 175,000 patient years, the number of cases of subacute severe liver impairment leading to liver transplantation with Esmya is higher than expected (4 transplantation cases among 175,000 patient years - a total of 7 cases with severe liver impairment among 175,000 patient years; although causality is uncertain for some of these cases).

Although firm conclusions cannot be drawn that these cases were caused by Esmya, the available data raise serious concerns. While the magnitude and nature (e.g. pattern of hepatotoxicity and possible mechanism of action) of the risk are being reviewed in depth, having considered the seriousness of the risk, the PRAC considered that the above raised a reasonable doubt that justifies adopting provisional measures in the meantime.

The PRAC considered the potential risk of hepatotoxicity of the product, together with the fact that Esmya is a symptomatic treatment and not curative, that has the potential to reduce the need for surgical intervention. The PRAC considered the duration of treatment with Esmya, the timelines of the current scientific evaluation and the patients that are currently under treatment. Considering all these factors, in order to recommend the measure that would be the most proportionate, the PRAC concluded to provisionally limit the use of the medicinal product to patients that are currently under therapeutic treatment. With regards to patients under intermittent treatment, the use of the medicinal product should not be repeated in patients who have finalised a previous treatment course. In addition, for patients currently under treatment, a monitoring of serum transaminases levels should to be performed at least monthly and immediately in case of incidence of signs and symptoms of liver injury. Patients exhibiting signs and symptoms suggestive of liver injury should promptly contact a healthcare professional. Liver monitoring should also be performed up to four weeks after the discontinuation of the treatment. Healthcare Professionals (HCPs) should be informed of the cases of liver injury and hepatic failure reported with the use of Esmya in post-marketing experience. The threshold of transaminases elevation for patients not included in clinical trials, which is two times the upper limit of normal, should be considered as the threshold in which the discontinuation of treatment is recommended. Patients overcoming such threshold should be closely monitored after discontinuation of the treatment.

The above provisional measures should be reflected in the terms of the marketing authorisation, including the product information of Esmya, and communicated to HCPs via a DHPC. The adequacy of these provisional measures will be reviewed as part of the ongoing Article 20.

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), in particular the need for provisional measures in accordance with Article 20(3) of Regulation (EC) N0 726/2004.
- During the ongoing review of safety and efficacy data in relation to the overall risk of liver injury with Esmya, the PRAC reviewed all data currently available from post-marketing settings and from clinical trials as well as the responses provided by the marketing authorisation holder on cases of serious liver injury reported with Esmya.
- The PRAC noted that four cases of acute liver failure leading to liver transplantation including one with fatal outcome have been reported with Esmya. PRAC concluded that the use of Esmya could potentially be associated with a risk of serious liver injury. In view of the seriousness of the cases, the PRAC considered that provisional measures are now needed to minimise this risk and protect patients, while the review is ongoing and a thorough assessment of all available data related to the benefit-risk of Esmya is performed.
- The PRAC recommends that no new patients should be treated with the medicinal product while the review is ongoing. The provisional measures proposed by PRAC also include the limitation of use of the medicinal product in patients that are currently under therapeutic treatment. With regards to patients under intermittent treatment, the use of the medicinal product should be discontinued in patients who have finalised a previous treatment course.
- PRAC recommended monitoring of the liver function at least monthly of patients under treatment as well as up to four weeks after the discontinuation of the treatment. These investigations should occur immediately in case a patient shows signs or symptoms compatible with liver injury. Patients who develop transaminase levels > 2 times the upper level of normal during Esmya treatment should stop treatment and be closely monitored.
- Furthermore, PRAC recommended that a healthcare professional communication should be disseminated to inform healthcare professionals about the precautionary measures, awaiting the outcome of the full review of Esmya.

In view of the above, the Committee considers that the benefit-risk balance of Esmya remains favourable subject to the agreed provisional measures.

The Committee, as a consequence, recommends the variations of the terms of the marketing authorisation for Esmya.

This recommendation is without prejudice to the final conclusions of the ongoing procedure under Article 20 of Regulation (EC) No 726/2004.