Annex IV

Scientific conclusions

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On 7 June 2017, the European Commission (EC) was informed of a fatal case of fulminant liver failure in a patient treated with daclizumab in an ongoing observational study, despite monthly liver function testing performed in accordance with recommendations in the product information. In addition 4 cases of serious liver injury were reported from clinical trials, in the first periodic safety update report (PSUR).

Transaminases elevations and serious hepatic injury are known risks associated to treatment with Zinbryta (daclizumab) and several risk minimisation measures (RMMs) were implemented in this regard, including monthly liver function monitoring. However, in view of the seriousness of the reactions reported, leading in one case to a fatal outcome despite adherence to the recommended RMMs, the EC considered that the impact of the risk of liver injury on the benefit-risk balance of the medicinal product and the adequacy of the related RMMs should be reviewed.

On 9 June 2017 the EC therefore 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 Zinbryta (daclizumab) and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked. In addition, the EC requested the Agency to give its opinion, as to whether provisional measures were necessary to protect public health. The current recommendation relates only to provisional measures recommended by the PRAC for daclizumab based on the preliminary data available at this time.

Overall summary of the scientific evaluation by the PRAC

Zinbryta (daclizumab) is a centrally authorised medicinal product indicated in adult patients for the treatment of relapsing forms of multiple sclerosis (RMS).

The PRAC considered the preliminary new safety data from a recent fatal case of fulminant liver failure and from cases of serious liver injury that occurred since the marketing authorisation, in the context of the data generated during the clinical development of daclizumab.

The efficacy of daclizumab was demonstrated in two pivotal studies in subjects with relapsing remitting multiple sclerosis that led to the indication in relapsing multiple sclerosis. During the clinical development, transaminases elevations and serious hepatic injury were identified as important identified risks. The majority of findings were asymptomatic transaminases elevations, however a low incidence of serious liver events and a rare incidence of fatal liver failure (autoimmune hepatitis) were acknowledged as important risks with daclizumab. Since the initial marketing authorisation further serious cases of liver injury have been reported, including a fatal case despite an attempted liver transplant. Notable for this fatal case was the occurrence of rapid fulminant liver failure in the setting of recommended liver function monitoring and concomitant use of another medicinal product known to be associated with hepatotoxicity.

The RMMs implemented, in particular the monthly liver testing, have not been effective to prevent the fatal case of fulminant hepatic failure. While liver function monitoring continues to be an important measure to detect liver injury, and likely reduce the incidence of severe cases, it is unclear at this stage whether any alternative monitoring regimen would necessarily prevent further severe cases. Therefore, while the magnitude and nature of the risk are being reviewed in depth, having considered the seriousness of the risk and that further RMMs that would be effective in preventing with certainty any new severe cases cannot be identified at this stage, the PRAC considered that it is necessary to provisionally limit the use of daclizumab through restriction of the indication and through preventing its use in patients potentially predisposed to liver injury and provide further recommendations to healthcare professionals (HCPs) and patients in the management of this risk.

The PRAC took under consideration the alternative treatment options for the different stages or manifestations of RMS and that limiting access to daclizumab may deny some patients a treatment option for this disease. Further, the PRAC took into consideration that interrupting treatment in patients whose disease is well-controlled with daclizumab may induce relapses. Thus, considering the serious risk of hepatic injury along with the benefit that daclizumab may bring to RMS patients, the PRAC recommended that the use of daclizumab should be provisionally restricted to adult patients with highly active RMS despite a full and adequate course of treatment with at least one disease modifying therapy (DMT) or, with rapidly evolving severe relapsing multiple sclerosis who are unsuitable for treatment with other DMTs.

The PRAC noted that the hepatic findings observed during the clinical development program had led at time of the initial marketing authorisation to the inclusion of a warning in the product information that treatment of patients with pre-existing severe hepatic impairment is not appropriate and that those with pre-existing mild or moderate hepatic impairment should be monitored. Considering the lack of clinical data in patients with pre-existent significant hepatic diseases as these were excluded from clinical trials, the new serious hepatic cases, and that a mild elevation of serum transaminases was reported prior to treatment initiation in the patient who died of fulminant liver failure, the PRAC recommended as a provisional measure that daclizumab should be contraindicated in all patients with pre-existing hepatic disease or hepatic impairment, while the pattern of hepatotoxicity and possible mechanism of action is further investigated.

In view of the restricted indication and contraindication in patients with pre-existing hepatic disease or hepatic impairment, the PRAC recommended that physicians should re-evaluate promptly whether daclizumab continues to be an appropriate treatment option for each of their patients currently treated with this medicinal product, taking into account the provisional measures recommended by the PRAC.

In the fatal case under review, the finding of normal serum transaminases levels prior to the dose of daclizumab did not prevent the occurrence of liver failure. Therefore, monitoring of serum transaminases levels should continue to be performed at least monthly and more frequently as clinically indicated, further, bilirubin levels should also be tested. In addition, prompt recognition of signs and symptoms of liver injury is a key component of risk minimisation for liver injury with daclizumab and these should be monitored in all patients. Patients exhibiting signs and symptoms suggestive of liver injury should be promptly referred to a hepatologist.

Analyses performed in the clinical development program to assess potential interactions of daclizumab with potentially hepatotoxic medications showed no clear evidence of increased risk of liver injury with concomitant hepatotoxic medications. However, a number of serious hepatic events in patients in daclizumab groups occurred in the setting of concomitant drugs with known hepatotoxic potential, including one fatal autoimmune hepatitis and one non-fatal hepatic failure assessed by an adjudication committee as probable Hy's Law (indicative of a risk of drug-induced severe liver injury). This was also noted in serious cases that occurred since the marketing authorisation, including the fatal case, therefore while the role of concomitant hepatotoxic medication is not fully elucidated, concomitant use with daclizumab should be cautious. It was also noted that autoimmune thyroiditis was reported in the recent fatal case as well as in one of the Hy's law adjudicated cases; therefore treatment initiation is not recommended in patients with history of concurrent autoimmune conditions. Finally, physicians should consider discontinuing daclizumab treatment if an adequate therapeutic response has not been achieved.

HCPs and patients should be informed of the post-marketing fatal case of fulminant liver failure, the common risk of hepatitis and the updated frequency of serious cases of hepatic injury in the light of the new cases. Cases of serious liver injury occurred at any time point between early after treatment initiation to several month after discontinuation and no window of susceptibility to could be defined

from cases observed in clinical trials. The threshold of transaminases elevation for patients not included in clinical trials, and therefore in which treatment initiation is not recommended, should be corrected from above two times the upper normal limit to above or equal to two times that limit.

The above provisional measures should be reflected in the product information of daclizumab and communicated to HCPs via a dedicated letter. 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, in particular regarding the need for provisional measures in accordance with Article 20(3) of Regulation (EC) No 726/2004 for Zinbryta (daclizumab).
- The PRAC reviewed the preliminary data provided by the marketing authorisation holder on cases of serious liver injury reported since the initial marketing authorisation, in the context of available safety data from clinical trials submitted in support of the initial marketing authorisation in relation to the overall risk of liver injury with daclizumab.
- The PRAC noted that a fatal case of fulminant liver failure occurred despite adherence to the terms of the marketing authorisation and the risk minimisation measures recommended, including the liver function monitoring. In view of this and while the magnitude and nature of the risk of liver injury is being further investigated, the PRAC considered that provisional measures are needed to limit the use of daclizumab.
- The PRAC recommended as provisional measure amendment to the indication of daclizumab to restrict its use to adult patients with highly active relapsing disease despite a previous treatment with at least one disease modifying therapy (DMT) or, with rapidly evolving severe relapsing multiple sclerosis who are unsuitable for treatment with other DMTs. The PRAC also considered that daclizumab should be contraindicated in patients with pre-existing hepatic disease or impairment.
- In addition, the PRAC recommended, as provisional measures to further minimise the risk of liver injury, to strengthen the current warnings to take due account that all patients should be monitored for signs and symptoms of hepatic injury and that liver functions testing should be performed at least monthly, to promptly refer patients to an hepatologist in case of signs or symptoms suggestive of such injury and that treatment initiation is not recommended in patients with other autoimmune conditions. Caution should also be used when medicinal products of known hepatotoxic potential are used concomitantly. In addition, consideration should be given to discontinue treatment if an adequate therapeutic response is not achieved.

In view of the above, the Committee considers that the benefit-risk balance of Zinbryta (daclizumab) remains favourable subject to the agreed provisional amendments to the product information. The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for Zinbryta (daclizumab).

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