Annex IV

Scientific conclusions

Scientific conclusions

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 at the time of the initial marketing authorisation, 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 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 marketing authorisation should be maintained, varied, suspended or revoked.

Overall summary of the scientific evaluation by the PRAC

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

The PRAC considered all the data provided by the MAH on cases of liver injury that occurred since the marketing authorisation, including a recent fatal case of fulminant liver failure, as well as safety and efficacy data from clinical trials with daclizumab, in relation to the overall risk of liver injury with daclizumab. The PRAC also considered the views expressed by experts consulted during the course of the procedure (scientific advisory group (SAG) on neurology).

The efficacy of daclizumab was demonstrated in two pivotal studies in subjects with relapsing remitting multiple sclerosis (RRMS) that led to the indication in relapsing multiple sclerosis. Results from both studies demonstrated clinically meaningful and statistically significant reductions in relapse rate, the primary efficacy endpoint in each study. Daclizumab treatment also resulted in clinically meaningful slowing of the accumulation of neurological disability as measured by both clinician-assessed and patient-reported outcome measures. These clinical effects were supported by robust and substantial treatment effects in reducing all key brain magnetic resonance imaging (MRI) parameters of acute and chronic inflammatory and destructive central nervous system disease activity. Subgroup analyses of these studies, although of limited robustness, did not identify statistically significant differences in key efficacy outcomes in MS patients with high disease activity compared to patients with low disease activity.

The PRAC concluded that daclizumab is associated with a potentially fatal risk of immune-mediated liver injury. No time window of a higher risk could be identified and cases of liver injury have occurred throughout treatment and up to 6 months after the last dose of daclizumab. Risk or predictive factors that may play a role on the occurrence of liver damage such as comorbidities, relation with dose, timing, genetic or biochemical markers could not be identified by the PRAC or the SAG. Overall, considering the data available, the occurrence of daclizumab induced liver injury is considered to be unpredictable.

The occurrence of a fatal case of fulminant liver failure despite adherence to the risk minimisation measures implemented before this procedure, including monthly liver monitoring, was particularly

of concern. The PRAC thus considered that further measures to those implemented as part of the provisional measures were justified to minimise this risk and, in view of its unpredictable and potentially fatal nature, to limit the use of the medicinal product.

Taking into account the conclusions from the SAG that the use of the medicinal product should be restricted to patients who are unsuitable for treatment with other disease modifying therapies (DMTs), the PRAC considered that the identification of sub-groups within the target population (i.e. with highly active disease and with rapidly evolving severe disease) was not warranted and that the restriction of the use would apply to all patients with RMS who are unsuitable for treatment with other DMT. Therefore PRAC recommended that the indication of daclizumab should be restricted to the treatment of adult patients with RMS who have had an inadequate response to at least two DMTs and for whom treatment with another DMT is contraindicated or otherwise unsuitable.

In addition, considering the lack of clinical data in patients with pre-existent significant hepatic diseases as these were excluded from clinical trials, the seriousness of the hepatic adverse reaction, and the increased susceptibility of patients with basal hepatic disease to experience worsening of the hepatic impairment, the PRAC considered that daclizumab should be contraindicated in all patients with pre-existing hepatic disease or hepatic impairment.

It was also noted that autoimmune thyroiditis was reported in the recent fatal case as well as in one of the adjudicated cases. Considering that immune-mediated conditions and autoimmune conditions have been reported in clinical trials, that the effect of daclizumab on other autoimmune disorders and the role of such disorder on daclizumab-induced liver injury is unknown, as also highlighted by the SAG, the PRAC considered that daclizumab treatment should not be recommended in patients with history of concurrent autoimmune conditions other than multiple sclerosis.

Cases of liver injury were identified both through signs and symptoms and through laboratory values, therefore patient serum transaminase and total bilirubin levels should be monitored at least monthly and as close as possible before each administration, and more frequently if clinically indicated during treatment. As the risk has been shown to persist for up to six months after the last dose of daclizumab, this monitoring should be continued for the same period after the end of treatment. Although it was recognised that this measure has no predictive value on the risk of developing severe and potential fatal liver injury, the SAG considered that as a precautionary measure discontinuation of therapy should be recommended when patients levels of ALT or AST reach over 3 times the upper limit of normal. This view was supported by the PRAC who recommended that this stricter discontinuation criterion, regardless of bilirubin levels, should be applied. To complement the laboratory follow-up, it was considered key by the SAG and the PRAC, that patients should be informed about the risk of hepatic injury, and warned about signs or symptoms suggestive of hepatic dysfunction. If a patient develops such signs or symptoms suggestive of livery injury they should be promptly referred to a hepatologist. Patients should also be explained the importance of adhering to the periodic liver monitoring. To facilitate the discussion between physicians and patients on this topic and ensure patients have understood information provided on the risk, following the view of the SAG, the PRAC required the introduction of an acknowledgment form. The acknowledgement form needs to be provided by physicians to all patients, including those currently on treatment. Physicians should consider discontinuing therapy if an adequate response has not been achieved or the patient fails to follow the requirement for scheduled liver test monitoring.

Based on the limited data available, any synergistic hepatotoxic effects in patients taking concomitant hepatotoxic medications on the liver injury caused by daclizumab could not be fully elucidated. Daclizumab is not expected to be metabolised by the liver and the experts noted that it would be unfeasible to completely exclude hepatotoxic medications from the clinical management

of MS patients. The PRAC concluded therefore that caution should be exercised when using such medicines concomitantly with daclizumab.

Patients with hepatitis C virus (HCV) or hepatitis B virus (HBV) were excluded from clinical trials and no correlation has been established between pre-existing infections with these viruses and daclizumab-induced serious liver injury at present. In view of the uncertainties around the exact mechanism of action of the immune-mediated liver injury and as the risk of hepatitis B reactivation with daclizumab has not been characterised, the PRAC recommended that patients should be screened for these viruses prior to treatment initiation. Patients tested positive should be recommended to consult with a physician with expertise in the treatment of these conditions.

Autoimmune hepatitis and fulminant hepatitis should be added as adverse drug reactions to the product information respectively with the frequencies uncommon and not known. In addition the frequency of transaminase increases and liver function tests abnormal should be updated to very common. The description of hepatic injury in the product information should be brought up to date in line with current knowledge.

Finally 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 PRAC concluded that the benefit-risk balance remained positive, provided that Zinbryta is only used in the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) who have had an inadequate response to at least two disease modifying therapies (DMTs) and for whom treatment with another DMT is contraindicated or otherwise unsuitable and that changes are implemented in the product information to minimise the risk of serious liver injury. The existing educational materials should also be updated with these recommendations and complemented with an acknowledgement form.

Grounds for PRAC recommendation

Whereas,

- The PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data for Zinbryta (daclizumab).
- The PRAC reviewed the totality of the data provided by the marketing authorisation holder on cases of serious liver injury reported since the initial marketing authorisation and safety and efficacy data from clinical trials, in relation to the overall risk of liver injury with daclizumab. The PRAC also considered the views expressed by the scientific advisory group on neurology.
- The PRAC concluded that daclizumab is associated, during the treatment and for several months after the end of treatment, with an unpredictable and potentially fatal risk of immune-mediated liver injury. The PRAC noted that a fatal case had occurred despite the risk minimisation measures already implemented, including monthly liver monitoring. The PRAC thus considered that further measures are needed to minimise this risk including limiting the use of the product to situations where no other therapeutic options are suitable.
- As a consequence, the PRAC recommended restriction of the indication of daclizumab to the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) who have had an inadequate response to at least two disease modifying therapies (DMTs) and for whom treatment with another DMT is contraindicated or otherwise unsuitable. The PRAC also considered that daclizumab should be contraindicated in patients with pre-existing hepatic disease or impairment.

- In addition, the PRAC recommended strengthening the current warnings to take due account that liver functions, including bilirubin levels, of all patients should be monitored at least monthly, close to each administration of daclizumab, and for six months after end of treatment and stricter discontinuation criteria in case of elevated transaminase should now be applied. Discontinuation should also be considered if an adequate response has not been achieved or if the liver function monitoring is not adhered to. Furthermore, PRAC recommended that all patients are informed about signs or symptoms suggestive of liver dysfunction and promptly referred to a hepatologist in case of such signs or symptoms.
- In addition, prior to treatment initiation, patients should be screened for hepatitis B and C infection and initiation is not recommended in patients with other autoimmune conditions. Administration of daclizumab with other medicinal products of known hepatotoxic potential should be done with caution.
- The PRAC also considered it necessary to introduce an acknowledgement form to ensure patients have been adequately informed on the risks of liver injury associated to daclizumab. The educational material in place should also be updated.

In view of the above, the Committee considers that the benefit-risk balance of Zinbryta (daclizumab) 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 Zinbryta (daclizumab).

CHMP opinion

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

The CHMP discussed the recommended wording of the indication, in particular that restricting daclizumab treatment to patients for whom another disease modifying therapy is contraindicated or otherwise unsuitable, and considered that for clarity it should be stated that this relates to any other disease modifying therapy. The CHMP concluded that the summary of products characteristics should be amended accordingly.

Overall conclusion

The CHMP, as a consequence, considers that the benefit-risk balance of Zinbryta (daclizumab) remains favourable subject to the amendments to the product information described above.

Therefore the CHMP recommends the variation to the terms of the marketing authorisations for Zinbryta (daclizumab).