Annex IV

Scientific conclusions

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On 10 March 2016, the European Commission was informed that an increased risk of death and higher incidence of serious adverse events (SAE) among subjects receiving idelalisib compared to the control groups had been observed in three clinical trials by the Independent Safety Data Monitoring group. The trials evaluated combinations with chemotherapy and immunotherapy which are currently not authorised for Zydelig (idelalisib), or authorised combination of Zydelig and immunotherapy but in a population with earlier disease characteristics than the currently approved indication. However, in light of the emerging safety data, the European Commission (EC) considered that the findings from the clinical trials and all available safety data related to idelalisib should be reviewed in order to assess their potential impact on the benefit-risk balance of Zydelig in the approved indications and relevant ongoing variations.

On 11 March 2016 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 Zydelig (idelalisib) and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked. In addition, the European Commission 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 idelalisib. It is to be noted that the data currently available to the PRAC is very limited and does not enable the PRAC to give definite conclusions. Therefore, provisional measures are recommended but these are without prejudice of the outcome of the ongoing review under Article 20 procedure.

Overall summary of the scientific evaluation by the PRAC

Zydelig (Idelalisib) is a centrally authorised product and is currently indicated in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy, or as first line treatment in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy. Idelalisib is also indicated as monotherapy for the treatment of adult patients with follicular lymphoma (FL) that is refractory to two prior lines of treatment.

The PRAC considered the very limited new safety data from three studies (GS-US-312-0123, GS-US-313-0124, GS-US-313-0125), now terminated, evaluating the addition of idelalisib to standard therapies in first line CLL and relapsed indolent non-Hodgkin lymphoma (iNHL)/small lymphocytic lymphoma (SLL). Interim results of these studies have shown an increased risk of death and serious adverse events in the idelalisib treatment arms compared to placebo. The PRAC noted that in study -0123, idelalisib was administered in combination with bendamustine and rituximab (which is not an authorised combination) and CLL patients were previously untreated, which is not consistent with the current CLL indication. Similarly, studies -0124 and -0125 are not consistent with the FL indication because idelalisib was combined with rituximab or rituximab and bendamustine, respectively, which are not authorised combinations.

The impact of the new safety findings in the currently authorised indications and extension of indication for use in CLL in combination with ofatumumab cannot be evaluated with certainty at present in view of the limited data available. Furthermore, in depth assessment is needed to firmly establish factors that may have driven death rates and it is too early to conclude that the risk is most apparent in the first 6 months. Notwithstanding this fact, the PRAC considered that the limited data available justified the recommendation of temporary measures to ensure that

healthcare professionals and patients are aware of the risks and of the measures to mitigate those. The PRAC therefore proposed risk minimisation measures, including amendments to the product information and a communication to healthcare professionals. As only very limited data is available, these measures are only temporary and are without prejudice to the ongoing review under Article 20.

The PRAC took into account the data submitted by the marketing authorisation holder (MAH). The MAH suggested that in studies -0123, -0124 and -0125 lines of therapy (i.e. increased risk in earlier stages of disease) and concomitant medication (such as bendamustine) may have increased the risk of infection. The reason why patients in the earlier stages of disease might be at increased risk of death and serious infection with idelalisib is not clear, although it is likely that there is an interaction between benefit-risk balance in differing populations and their level of disease-related mortality. As a temporary measure, the PRAC recommended that idelalisib should not be initiated as a first line treatment in CLL patients with 17p deletion or *TP53* mutation. For CLL patients with 17p deletion or *TP53* mutation already on idelalisib therapy as first line, clinicians should carefully consider individual benefit-risk balance and decide whether to continue treatment. Further, if continuing with therapy, new risk minimisation (see below) should be implemented. These temporary measures may be revised in light of the data that will become available and will be assessed in the ongoing Article 20 procedure, as the precise factors for the differences in safety outcomes between the three new studies (0123, -0124 and -0125) and those observed in studies supporting the initial marketing authorisation and proposed extension of indication for use in CLL in combination with ofatumumab.

Based on the inhibitory effects of idelalisib on the PI3K pathway, it is possible that the increased risk of serious infection observed in studies 0123, -0124 and -0125 could be relevant to the authorised indications. Also, post-marketing reports of adverse events in EudraVigilance indicate that infections (including sepsis and pneumocystis) account for a large proportion of reported cases, including fatal cases. Therefore, the PRAC recommended that idelalisib should not be initiated in patients with any evidence of ongoing systemic bacterial, fungal, or viral infection. Further measures to minimise the risk of infection should also be carried forward to clinical practice, including those used in studies supporting the initial marketing authorisation application with favourable results. These include:

- prophylaxis for *Pneumocystis jirovecii* pneumonia (PJP) to all patients throughout treatment;
- monitoring for respiratory signs and symptoms of throughout treatment and reporting of new respiratory symptoms;
- regular clinical and laboratory screening for cytomegalovirus (CMV) infection. Idelalisib treatment should be discontinued in patients with evidence of infection or viraemia;
- monitoring of absolute neutrophil counts (ANC) in all patients at least every two weeks for the first six months of treatment with idelalisib, and at least weekly in patients while ANC is less than 1,000 per mm3. A table to guide physicians was proposed for the posology section.

These recommendations should be reflected in the product information and communicated to healthcare professionals via a dedicated letter. These measures will be further reviewed as part of the ongoing Article 20.

Grounds for PRAC recommendation

Whereas,

- The PRAC considered the provisional measure under Article 20(3) of Regulation (EC) No 726/2004 in the framework of Article 20 of Regulation (EC) No 726/2004 procedure resulting from pharmacovigilance data for Zydelig (idelalisib).
- The PRAC reviewed the very limited and preliminary data provided by the marketing authorisation holder on the interim results of study GS-US-312-0123, GS-US-313-0124, GS-US-313-0125 that suggested an increased risk of death and serious infection with idelalisib. The PRAC also considered available safety data from clinical trials submitted in support of the initial marketing authorisation and extensions of indication and Eudravigilance data in relation to the overall risk of treatment with idelalisib.
- The PRAC noted that the use of idelalisib in studies -0123, -0124 and -0125 was in different conditions than those currently authorised, and at earlier stages of the diseases. Although the potential impact of these new safety findings in the current authorised indications is presently unknown, the PRAC recommended provisional amendments of the indication of idelalisib and considered that as a precautionary measure, idelalisib should not be initiated as a first line treatment in CLL patients with 17p deletion or *TP53* mutation. However, the committee recommended that idelalisib could be used for continuing treatment in those patients who had already initiated the medicine as first line treatment based on individual benefit-risk balance assessment and with the addition of new risk minimisation measures.
- The PRAC noted that most of the serious adverse events reported in studies 0123, -0124 and -0125 were related to infections. Whilst the matter is being further reviewed, the PRAC recommended as a provisional measure an update of the posology and warnings to take due account that treatment should not be initiated in patients with systemic infections, patients should be monitored for respiratory symptoms and be administered *Pneumocystis jirovecii* pneumonia prophylaxis. Regular clinical and laboratory screening for cytomegalovirus should also be performed. In addition, given the higher risk for infection, advice on dose reduction or treatment interruption in the event of severe neutropenia was also proposed.

In view of the above, the Committee considers that the benefit-risk balance of Zydelig remains favourable subject to the agreed provisional amendments to the product information and other risk minimisation measures. This recommendation is without prejudice to the final conclusions of the ongoing procedure under Article 20 of Regulation (EC) 726/2004.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for idelalisib.